Risk Factors Associated With Carbapenem-Resistant *Pseudomonas aeruginosa*

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ABSTRACT

Introduction: *Pseudomonas aeruginosa* infections resistant to carbapenem antimicrobials have increased. Traditional risk factors for non-carbapenem resistance include intensive care unit stay, mechanical ventilation, previous hospitalization, and major comorbidities. As microbes evolve, our understanding of their risk factors for resistance also should evolve.

Methods: We conducted a retrospective study of adult inpatients and outpatients with a positive *Pseudomonas aeruginosa* culture during 2014. Cultures were obtained from system laboratories and medical records were reviewed through our electronic medical record. Pearson's chi-squared test with Yates correction and 2-sample t-tests were performed on categorical and continuous variables, respectively. Binary regression was used for multivariable modeling.

Results: Patients (N=1,763), of mean age 68.0 years and body mass index (BMI) 30.4 kg/m^2, were more likely to be women (51.3%) and were predominately white (89.3%). Resistance to imipenem or meropenem (14.0%) on univariable analysis was associated with several variables of interest. Non-white race (odds ratio [OR] =1.67; *P*=0.009), respiratory cultures (OR=1.95; *P*=0.003), recent institutional transfer (OR=2.50; *P*<0.0001), vasopressor use (OR=1.98; *P*=0.001), central line placement (OR=1.55; *P*=0.036), and peripherally inserted central catheter placement (OR=1.74; *P*=0.002) remained significant predictors of carbapenem resistance in multivariable modeling.

Conclusion: Demographic and traditional risk factors, as well as respiratory cultures, were predictive of carbapenem resistance and may guide initial antibiotic treatment. Use of "last resort" antibiotics for *Pseudomonas aeruginosa* based solely on patient chronic conditions may not be necessary. Fortunately, <1% of strains were resistant to all drugs tested. Ongoing efforts to face drug-resistant organisms are warranted.

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INTRODUCTION

Over the last decade, infections with gram-negative bacteria have become a growing global concern due to increased resistance to widely accepted empiric therapies and new resistance mechanisms.[1-3] *Pseudomonas aeruginosa* (*P aeruginosa)* is a common gram-negative bacteria associated with nosocomial infections.[2-5] In 2013, an estimated 51,000 healthcare-associated *P aeruginosa* infections occurred in the United States, of which more than 13% were secondary to multidrug-resistant strains that resulted in nearly 400 deaths.[6] Infections with multidrug-resistant *P aeruginosa* have been correlated with higher treatment costs, increased mortality/morbidity, and additional care needs (ie, discharge to chronic care facilities).[2,3,5]

Risk factors for acquiring resistant organisms like *P aeruginosa* vary depending on patient characteristics and temporospatial factors.[1,2] Studies suggest that traditional risk factors for the acquisition of multidrug-resistant organisms include intensive care unit (ICU) admission, use of invasive medical devices (ie, mechanical ventilation), previous treatment with broad spectrum antibiotics (like cephalosporins, aminoglycosides, or carbapenems), length of hospital stay, and underlying diseases or comorbidities.[1,2,4,5,7]

Limited studies have investigated whether these risk factors for multidrug resistance can be used to predict carbapenem resistance in patients diagnosed with *P aeruginosa*.[8] As microbes evolve, our understanding of their risk factors also should evolve. This study aimed to determine whether traditional risk factors were predictive of carbapenem-resistant *P aeruginosa*.

METHODS

Study Design

We retrospectively studied all adult patients (inpatients and outpatients) with a positive *P aeruginosa* culture during the 2014 calendar year who presented to any of the 15 hospitals and 159 outpatient clinics in the Aurora Health Care system, an integrated medical system located primarily within eastern Wisconsin. Patients with a positive *P aeruginosa* culture were identified by ACL Laboratories, and culture site and antimicrobial susceptibility test records were obtained. The study population was inclusive of both colonized and infected patients with *P aeruginosa*. There was no way to differentiate colonization or infection based on culture results. Patient characteristics and demographics were obtained through Aurora Research Analytics and reviewed through the electronic medical record. Duplicate patient records were excluded and only the most recent positive culture susceptibility results were included in the analysis for each patient. The Aurora Institutional Review Board approved this study.

The outcome of interest, carbapenem-resistant *P aeruginosa*, was defined as resistance to either imipenem or meropenem as identified by antimicrobial susceptibility testing. Ertapenem was not included in this definition as it is not an effective treatment against *Pseudomonas*.[9] Additionally, multidrug-resistant *P aeruginosa* was defined as resistance to ceftazidime, cefepime, aztronam, ciprofloxacin, piperacillin, and gentamicin.[4] For the purpose of this study, pandrug-resistant *P aeruginosa* was defined as resistance to the 6 traditional non-carbapenem drugs associated with multidrug-resistant *P aeruginosa* and both carbapenems. These definitions were also based on antimicrobial susceptibility testing.

Variables hypothesized as risk factors for carbapenem-resistant *P aeruginosa* included age, race/ethnicity, history of chronic medical conditions, history of infections with other multidrug-resistant pathogens, recent ICU stay, recent transfer from an institution, and recent procedures that may require a hospital stay. Race/ethnicity was categorized into 4 groups: white non-Hispanic, black non-Hispanic, white Hispanic, and other. Due to the low number of patients who identified as either Asian, Alaskan native or American Indian, and 2 or more race/ethnicities, they were categorized as other race/ethnicity. Data also were categorized by institutional source of the culture, including 14 system hospitals and the one system-wide network of clinics. Recent events (ie, ICU admission) were identified from electronic medical record encounters and were defined as events that occurred up to 1 year prior to the most recent culture positive for *P aeruginosa*. Additionally, we hypothesized that cultures obtained within a hospital facility for inpatient or emergency department care also may be associated with resistance.

Statistical Analysis

Analyses were performed using MINITAB statistical software (Version 13; State College, PA). To describe demographic characteristics of our study population, frequencies with percentages and odds ratios (OR) with 95% confidence intervals (CI) were computed. To determine which risk factors were predictive of carbapenem resistance, we used the Pearson chi-squared test of independence with Yates correction and 2-sample t-tests, as appropriate. Significance was defined as $P< 0.05$. Only variables demonstrating significance in univariable analyses were included in multivariable logistic regression models. A P value cutoff of <0.20 for single variables was also explored to minimize bias associated with a P value cut off of <0.05.[10]

RESULTS

During the study period, data were collected on a total of 1,763 inpatients and outpatients with a positive *P aeruginos*a culture who met inclusion criteria. Across all of those identified with *P aeruginosa*, patients of mean age of 68.0 years and BMI 30.4 kg/m^2, were predominately white (89.3%), more likely to be women (51.3%), and from the outpatient setting (51.5%). *P aeruginosa* was isolated from non-respiratory surface or deep body tissue sites (44.9%), urinary tract (42.8%), respiratory tract (9.9%), and blood (2.4%).

Overall, 14.0% of cultures were resistant to imipenem or meropenem and were deemed carbapenem-resistant. Univariable analyses identified several variables that were significantly associated with carbapenem resistance (Table 1). Multivariable analyses revealed that the odds of carbapenem resistance were greater among those with a respiratory culture and who were of black or non-Hispanic race, as well as those who had a recent transfer from an institution, vasopressor use, central line placement, and peripherally inserted central catheter placement. All predictors remained in the multivariable model when single variables with a P value <0.20 were included.

While a mixture of inpatient and outpatient culture sources were present in each of the 14 system hospital locations, the proportions of carbapenem-resistant strains varied widely from a low of 3/58 (5.2%) at a small suburban Milwaukee County hospital to a high of 114/488 (23.36%) at a large, tertiary Milwaukee hospital. The proportion of resistant strains was 30/535 (5.6%) in cultures obtained system-wide from our outpatient clinic network. Despite these differences, when location of culture source was added to models or substituted for inpatient versus outpatient status, with either the tertiary hospital or the clinic network used as a reference "location," there was no significant change to the multivariable results listed in Table 1, with the exception of black race, which changed from borderline significant (P=0.042) to nonsignificant (P=0.06).

Overall, 9.0% of strains were resistant to both imipenem and meropenem. Additionally, only 0.62% and 0.57% of strains were deemed multidrug-resistant and pandrug-resistant *P aeruginosa*, respectively.

Table 1. Predictors of Carbapenem-Resistant *Pseudomonas aeruginosa* on Univariable and Multivariable Analyses

	Carbapenem-Resistant *P aeruginosa*					
Predictors	**Resistant (N=246)**	**Nonresistant (N=1517)**	**Univariable OR (95% CI)**	**Univariable *P* value**	**Multivariable OR (95% CI)**	**Multivariable *P* value**
Demographic Characteristics		68.3				
Younger Age (years), mean (SD)[a]	65.9 (15.5)	(16.8)	0.99 (0.98-1.00)	0.027	0.99 (0.98-1.00)	0.108
BMI (kg/m2), mean (SD)[a]	30.7 (11.1)	30.3 (9.7)	1.00 (0.99-1.02)	0.671	--	--
Male, N (%)	138 (56.1)	723 (47.7)	1.40 (1.07-1.84)	0.017	1.22 (0.91-1.64)	0.191
Race/Ethnicity[b]		1316				
White, non-Hispanic	185 (77.1)	(88.0)	*ref*	*ref*	*ref*	*ref*
Black, non-Hispanic	36 (15.0)	119 (8.0)	2.15 (1.44-3.22)	<0.0001	1.61 (1.02-2.55)	0.042
White Hispanic	11 (4.6)	36 (2.4)	2.17 (1.09-4.34)	0.028	1.84 (0.87-3.89)	0.113
Other	8 (3.34)	24 (1.61)	2.37 (1.05-5.36)	0.038	1.61 (0.63-4.11)	0.324
Hospitalized patients, N (%)	168 (68.3)	687 (45.3)	2.60 (1.95-3.47)	<0.0001	1.20 (0.85-1.72)	0.303
Culture Type						
Nonrespiratory surface or deep tissue culture, N (%)	103 (41.9)	688 (45.4)	*ref*	*ref*	*ref*	*ref*
Respiratory culture, N (%)	54 (22.0)	121 (8.0)	2.98 (2.03-4.37)	<0.0001	1.80 (1.13-2.88)	0.013
Blood culture, N(%)	7 (2.9)	35 (2.3)	1.34 (0.58-3.09)	0.498	1.08 (0.43-2.70)	0.875
Urine culture, N (%)	82 (44.4)	673 (33.3)	1.23 (0.90-1.67)	0.191	1.20 (0.83-1.72)	0.323
History of:						
Diabetes mellitus, N (%)	97 (39.4)	527 (34.7)	1.22 (0.93-1.61)	0.153	--	--
Stage 4 or 5 kidney disease, N (%)	79 (32.1)	412 (27.2)	1.27 (0.95-1.70)	0.108	--	--
Chronic obstructive pulmonary disease, N (%)	55 (22.4)	229 (15.1)	1.62 (1.16-2.26)	0.005	1.09 (0.74-1.60)	0.679
Congestive heart failure, N (%)	54 (22.0)	236 (15.6)	1.53 (1.10-2.13)	0.016	1.13 (0.77-1.65)	0.535
Infections with other multidrug-resistant pathogens, N (%)	11 (4.5)	22 (1.5)	3.18 (1.52-6.65)	0.003	1.89 (0.84-4.27)	0.126
Recent Events						
Transfer from an institution, N (%)[c]	119 (48.4)	352 (23.3)	3.09 (2.34-4.08)	<0.0001	2.52 (1.80-3.52)	<0.0001
Chronic steroid use, N (%)	2 (0.8)	17 (1.1)	0.72 (0.17-3.15)	0.665	--	--
Surgery, N (%)[d]	100 (40.7)	461 (30.5)	1.56 (1.18-2.06)	0.002	1.14 (0.83-1.57)	0.412
Foley catheter placement, N (%)	133 (54.1)	535 (35.3)	2.16 (1.65-2.84)	<0.0001	1.15 (0.82-1.61)	0.412
Vasopressor treatment, N (%)	93 (37.8)	190 (12.5)	4.25 (3.15-5.73)	<0.0001	1.96 (1.28-2.99)	0.002
Central line placement, N (%)	99 (40.2)	242 (16.0)	3.55 (2.66-4.74)	<0.0001	1.55 (1.03-2.33)	0.035
Peripherally inserted central catheter, N (%)	157 (63.8)	494 (32.6)	3.65 (2.76-4.84)	<0.0001	1.69 (1.18-2.40)	0.004
Mechanical ventilation, N (%)	34 (13.8)	78 (5.1)	2.96 (1.93-4.54)	<0.0001	1.04 (0.62-1.75)	0.875
ICU admission, N (%)	146 (59.4)	524 (34.5)	2.77 (2.10-3.64)	<0.0001	1.18 (0.79-1.75)	0.408
Dialysis, N (%)	38 (15.5)	190 (12.5)	1.28 (0.87-1.86)	0.205	--	--
Bedridden status, N (%)[e]	61 (24.8)	161 (10.6)	2.77 (1.99-3.87)	<0.0001	1.20 (0.81-1.78)	0.368

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; ICU, intensive care unit.
[a] Continuous variable.
[b] Missing variables of interest; numbers used for analysis: Resistant (N=240) and Nonresistant (N=1495).
[c] Missing variables of interest; number used for analysis: Nonresistant (N=1514).
[d] Missing variables of interest; number used for analysis: Nonresistant (N=1513).
[e] Missing variables of interest; number used for analysis: Nonresistant (N=1515).

DISCUSSION

Several studies have identified respiratory culture sites as an independent risk factor for infections with *P aeruginosa*.[3,11,12] The flagellar cap and outer core of lipopolysaccharide molecules of *P aeruginosa* are advantageous for adhesion to mucins within the lungs and rapid development of resistant strains.[13,14] Unsurprisingly, we found that carbapenem-resistant *P aeruginosa* was significantly associated with respiratory culture sites, which was consistent with the findings of Dantas et al.[12] As *P aeruginosa* is a common cause of ventilator-associated pneumonia,[14] we were surprised to find no association of multidrug-resistant *P aeruginosa* with mechanical ventilation on multivariable analyses. Patients requiring mechanical ventilation occasionally require other aggressive management modalities (ie, peripherally inserted central catheter, central line,

vasopressors, etc). It is possible that the risk for infections with resistant organisms in mechanically ventilated patients is only a perceived risk, given their disease state and treatments being utilized. Further studies of multidrug-resistant *P aeruginosa* in mechanically ventilated patients are warranted.

It is well known that healthcare facilities (ie, hospitals, subacute care facilities and nursing homes) provide an environment where selective pressure due to broad spectrum antibiotic use results in the selection of highly resistant pathogens.[4,5,15] Our findings of elevated risk for carbapenem-resistant *P aeruginosa* in patients who had a recent transfer from an institution were consistent with this phenomenon. Individual risk factors (vasopressor treatment, central line placement, and peripherally inserted central catheter placement) identified by Aloush et al for multidrug-resistant *P aeruginosa* were consistent with our findings for carbapenem-resistant *P aeruginosa* on both univariable and multivariable analyses.[4] Such invasive treatments are often reserved for very sick patients requiring invasive modalities for disease management. These patients may already have a compromised immune system due to disease burden, and added insult of invasive treatments provides pathogens with an opportunity for access. Additionally, invasive treatments may be proxies for length of stay, which may be an independent factor influencing the development of resistance. Further study is necessary.

Overall, there are many useful clinical implications that can be drawn from this study: (1) it is likely that the coalition of the above-mentioned risk factors, rather than individual factors, increase the risk of carbapenem resistant *P aeruginosa* infections; (2) patients who have multiple risk factors for resistance should minimize carbapenem use,[1,8] and empiric therapies from other antibiotic groups with known activity against *Pseudomonas* should be utilized; and (3) history of an infection with other resistant pathogens or chronic medical conditions were not risk factors for carbapenem-resistant *P aeruginosa*. Additionally, increased implementation of antibiotic stewardship programs is needed to ensure the appropriate use of antimicrobials in an effort to minimize the development and spread of drug resistance among microbes.[1,9]

Our study has several strengths. First, this study investigated a large cohort of individuals who had a positive *P aeruginosa* culture, giving us the statistical power needed to detect any effects or patterns associated with our outcome of interest. Thus, we were able to derive a stronger sense of what risk factors may predict or correlate with resistance. Identification of risk factors has become increasingly important within our specific region of Wisconsin, as *P aeruginosa* isolates seem to have decreased susceptibility, not only to carbapenems, when compared to other nearby regions.[16] Additionally, antimicrobial susceptibility testing was very comprehensive, allowing us to identify carbapenem, multidrug, and pandrug resistance. Secondly, even though in practice chronic medical conditions such as diabetes or chronic kidney disease are thought to increase the risk of resistance, this was not confirmed by our study. Our results may positively impact clinical practice by reducing unwarranted use of last resort antibiotics based solely on a patient's chronic conditions.

Our study also has some limitations. First, this was a retrospective study design in which information or observer bias could be introduced. Electronic medical records (EMR) are only as accurate as the recorder and not all data collected may be available. This is particularly true when identifying recent events (ie, surgery), as patients may not have had a documented surgery in our EMR if the surgery was conducted outside of our hospital system. Additionally, there could be sampling biases due to the nonrandom selection of the population studied, although all patients meeting criteria during the period were used. Further prospective studies are needed to minimize these biases. Secondly, this study focused on a population of individuals from a single hospital system and geographic region, which may impact the generalizability of our findings. Additionally, our study could not identify specific mechanisms associated with resistance given the retrospective study design.

CONCLUSION

Demographic and traditional risk factors, as well as isolation of *P aeruginosa* from respiratory culture sites, were predictive of carbapenem resistance. Further understanding of these risk factors with prospective studies and evidence-based scoring systems involving well studied risk factors, may provide an invaluable tool for the prevention and management of carbapenem resistant *P aeruginosa*. Emergence and spread of antimicrobial resistance is an increasing challenge among healthcare systems across the world. Ongoing efforts to face drug-resistant organisms are vital to the future care of patients.

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