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Antibiotic Resistance Rates for *Pseudomonas aeruginosa* Clinical Respiratory and Bloodstream Isolates Among the Veterans Affairs Healthcare System from 2009 to 2013

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Abstract

Pseudomonas aeruginosa is a major cause of healthcare-associated infections and resistance among isolates is an increasing burden. The study purpose was to describe national resistance rates for clinical *P. aeruginosa* respiratory and bloodstream cultures and the prevalence of multidrug-resistant (MDR) *P. aeruginosa* within the Veterans Affairs (VA). MDR was defined as non-susceptibility to at least one drug in at least 3 of the following 5 categories: carbapenems, extended-spectrum cephalosporins, aminoglycosides, and piperacillin/tazobactam. We reviewed 24,562 *P. aeruginosa* respiratory and bloodstream isolates across 126 VA facilities between 2009 to 2013. Most isolates were collected from inpatient settings (82%). Resistance was highest in fluoroquinolones (33%) and exceeded 20% for all classes assessed (carbapenems, extended-spectrum cephalosporins, aminoglycosides, and piperacillin/tazobactam). Resistance was higher in inpatient settings and in respiratory isolates. Prevalence of MDR was 20% overall (22% for inpatient isolates, 11% outpatient, 21% respiratory, 17% bloodstream). Our findings are consistent with previous surveillance reports

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Body of the Text

Introduction

Pseudomonas aeruginosa is a major cause of healthcare-associated infections.(1) *P. aeruginosa* is a leading cause of severe Gram-negative infections, including pneumonia and bloodstream infections, which are associated with high mortality rates.(2, 3) Antimicrobial resistance and multidrug-resistance (MDR) among *P. aeruginosa* isolates collected from hospitalized patients are increasing and threaten the appropriate treatment of patients with severe infections.(4, 5) *P. aeruginosa* is also an important cause of community-acquired pneumonia in patients with underlying lung disease, alcoholism and compromised immune function.(6-8) However, surveillance of isolates from the community is less frequent than from healthcare settings and nationwide resistance rates in community setting are less well understood.

The Veterans Affairs (VA) is the largest integrated healthcare system in the United States (US), providing care to approximately 9 million Veterans in 140 medical centers and 1200 outpatient clinics. Clinical antimicrobial susceptibility data from VA electronic datasets support a nationwide description of *P. aeruginosa* resistance.(9) The aim of this study was to assess national antibiotic resistance rates for clinical *P. aeruginosa* respiratory and bloodstream cultures, as well as determine the prevalence of MDR *P. aeruginosa* in the VA system.

Methods

We evaluated antimicrobial susceptibility from all VA hospitals, long-term care units and outpatient facilities in the United States.(9) We included all *P. aeruginosa* blood and respiratory clinical cultures collected between January 1, 2009 to December 31, 2013 from patients aged 18 years or older.

We defined antibiotic resistance per the CDC Antibiotic Resistance Patient Safety Atlas Phenotype Definitions.(10) We included the first isolate per person, per facility, per month.(10) Antibiotic susceptibility was based on the reported microbiology results of the clinical culture. As microbiology practices and susceptibility breakpoints are not standardized throughout the VA system, we applied the 2014 Clinical Laboratory Standards Institute (CLSI) breakpoints to determine non-susceptibility where numeric minimum inhibitory concentrations (MIC) data were available.(11) Where MIC values were not available, we used the reported textual interpretation (i.e., resistant [R], intermediate [I], or susceptible [S]).)(12) In cases of duplicate (same patient, same isolate, same day), yet conflicting antimicrobial susceptibility results, we included the most resistant result (i.e., R > I > S).(12)

We grouped individual antibiotic agents into five categories as follows: extended-spectrum cephalosporins (ceftazidime and cefepime); fluoroquinolones (levofloxacin and ciprofloxacin); aminoglycosides (amikacin, gentamicin, and tobramycin); carbapenems (imipenem, meropenem, and doripenem), and piperacillin/tazobactam (piperacillin and piperacillin/tazobactam).(10) Resistance was defined as an isolate that was not susceptible, thus either intermediate or resistant, to at least one drug in that category.(10) Multidrug-resistance (MDR) was defined as non-susceptibility to at least one drug in at least 3 of the 5 categories (extended-spectrum cephalosporins, aminoglycosides, carbapenems, and piperacillin/tazobactam).(10)

We presented summary rates of antibiotic resistance for each of the five antibiotic categories assessed and prevalence of MDR among *P. aeruginosa* isolates. Antibiotic resistance for each antibiotic category was calculated as the number of non-susceptible isolates divided by the total number of isolates tested. Prevalence of MDR was calculated as the number of MDR isolates divided by the total number of isolates tested. We presented overall rates of antibiotic resistance and MDR over the entire study period, and presented rates by treatment setting, source, and CDC region. All analyses will be performed with SAS (SAS, Cary, NC, Version 9.2).

Results

We identified 24,562 *P. aeruginosa* isolates from 126 VA facilities over the 5-year study period; 82% were from inpatient settings. Most isolates were obtained from white (72%), male (97%), Veterans 65 years and older (59%). Resistance was highest for fluoroquinolones (33%) and lowest for the piperacillin class (piperacillin/tazobactam and piperacillin, 21%; Table 1). Resistance to carbapenems, extended-spectrum cephalosporins, and aminoglycosides was 24-25%. Resistance was higher in inpatient settings (Table 1) and in respiratory isolates (Table 2). Prevalence of MDR was 20% overall (22% and 11% for inpatient and outpatient settings, respectively; and 21% and 17% for respiratory and bloodstream isolates, respectively).

Among inpatient cultures, resistance rates were highest in the Pacific region (fluoroquinolones 42%, carbapenems 35%, MDR 30%) and lowest in the Mountain (fluoroquinolones 27%, carbapenems 17%, MDR 14%) and New England regions (fluoroquinolones 27%, piperacillin class 17%, MDR 16%) (Figure 1). Outpatient resistance rates were highest in the Mid-Atlantic region (fluoroquinolones 31%, carbapenems 22%, MDR 21%) and lowest in the New England (fluoroquinolones 20%, carbapenems 10%, MDR 6%) and West South Central regions (fluoroquinolones 17%, carbapenems 11%, MDR 7%) (Figure 2).

Discussion

Treatment of *P. aeruginosa* infections are challenging due to intrinsic resistance and ability to develop resistance to multiple antimicrobial classes.(13, 14) These features limit treatment options and complicate selection of appropriate initial antibiotic treatment, which can have devastating consequences on patient outcomes.(14, 15) We observed rates of resistance in excess of 20% for all antimicrobial classes assessed. Our findings are similar to previous surveillance reports, and in some cases, resistance was higher in our study.(4, 5, 13) The most recent study of 7,452 *P. aeruginosa* isolates from 79 US medical centers between 2012 to 2014 demonstrated non-susceptibility of 20% for piperacillin-tazobactam, 18% for meropenem, and 16% for ceftazidime, compared to our findings of 24% resistance for piperacillin-tazobactam and piperacillin, 27% for carbapenem, and 27% for extended-spectrum cephalosporins.(13)

Prior surveillance data suggests a trend towards stabilized or decreased antimicrobial resistance to several agents among *P. aeruginosa* isolates in the US.(13, 16) Recent data from the VA system has demonstrated this trend in deceased antimicrobial resistance among *P. aeruginosa* isolates.(17) We observed similar resistance rates among bloodstream isolates to those previously reported. We also found higher resistance rates among nosocomial isolates and variations in resistance rates by CDC region.(17)

Overall, we demonstrated high rates of MDR among *P. aeruginosa* isolates (20%), with higher rates in the inpatient vs. outpatient setting (22% vs. 11% outpatient) and pulmonary vs. blood source (21% vs. 17% blood). National surveillance data from 2000 to 2009, including 205,526 *P. aeruginosa* isolates from pneumonia and bloodstream infections, demonstrated prevalence rates of MDR among *P. aeruginosa* isolates similar to our findings (22% for pneumonia; 15% for bloodstream infections).(4) Among bloodstream isolates in a recent VA study, there was a lower rate of MDR than we had observed.(17) Differences in methods used to define MDR likely explain variations in reported MDR rates. While we used the CDC Patient Atlas MDR definitions requiring non-susceptibility to at least one antibiotic in at least 3 different classes, the previous study required resistance to all antibiotics tested in at least 3 different classes.(17)

Finally, our results from the outpatient setting are noteworthy. None of the antimicrobial classes assessed provided greater than 10% anti-pseudomonal coverage and rates of MDR were 11% nationally (Table 1), exceeding 20% in the Mid Atlantic region (Figure 2). Inappropriate initial empiric antimicrobial treatment is thus an important concern in the treatment of community-onset *P. aeruginosa* infections. Inappropriate initial empiric antimicrobial treatment is common inpatients with community-acquired *P. aeruginosa* bloodstream infections and those with pneumonia and it is associated with greater mortality.(18, 19) While combination therapy remains controversial, it may be important approach to minimize inappropriate initial therapy, especially in regions with the highest resistance rates.

Our findings add to previous work, highlighting antibiotic resistance among *P. aeruginosa* isolates nationally. We demonstrated that resistance to five key and commonly used antimicrobial classes was high despite treatment setting, culture source, and region. Due to the poor outcomes associated with inappropriate treatment of severe *P. aeruginosa* isolates, facilities should consider developing treatment pathways or policies, which potentially include use of combination therapy and/or newer antimicrobial options, for infections in which MDR organisms are suspected. Additionally, knowledge of specific risk factors for resistant and MDR *P. aeruginosa* isolates would be important to help clinicians better care for patients with infections due to resistant pathogens, and is an important next step to this work. Finally, antimicrobial stewardship programs are mandated in the acute care setting in the VA, however increased efforts in the outpatient setting are warranted and urgently needed.(20) Increased assistance with antibiotic selection could help to manage these difficult to treat infections due resistant *P. aeruginosa* isolates and potentially improve patient outcomes.

There are limitations to this observational, cross-sectional work. The inclusion of all positive *P. aeruginosa* respiratory and blood cultures enabled us to describe ecological resistance in the VA system, however, we did not distinguish between colonization from true infection. Additionally, there is the potential for misclassification of community-acquired isolates, as we did not assess healthcare contact prior to outpatient culture date. Another limitation is that our definition of resistance was based on non-susceptibility. Therefore, isolates that were intermediate met our definition of resistance, and as such we may have overestimated true resistance. However, our definitions are consistent with those used by the CDC Patient Safety Atlas.(10) There is heterogeneity among microbiology laboratories in the VA system and different testing methods among labs may have impacted our findings. We applied CLSI susceptibility breakpoints where MIC data was available, however MIC data was not available for all isolates. In such cases we had to rely on the interpretation as provided by the testing microbiology laboratory. Finally, the generalizability of the study population and results are limited to the VA, a fully integrated healthcare system consisting of largely older, white male patients.

In summary, among nearly 25,000 clinical *P. aeruginosa* respiratory and bloodstream isolates, resistance to five key and commonly used antimicrobial classes (fluoroquinolones, carbapenems, extended-spectrum cephalosporins, aminoglycosides, and piperacillin group) exceeded 20% and 20% of isolates were MDR. Resistance was higher among isolates collected from the inpatient versus outpatient setting and from a respiratory source.

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Conflict of interest.

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Table 1. Antibiotic Resistance Rates for *Pseudomonas aeruginosa* Respiratory and Blood Cultures among Veterans Affairs Inpatient and Outpatient Facilities by Treatment Setting from 2009 to 2013

	Setting		
Antibiotic Category	Overall	Inpatient	Outpatient
Fluoroquinolones	33 (23,938)	36 (19,634)	23 (4,304)
Carbapenems	25 (21,176)	27 (17,424)	15 (3,752)
Extended-spectrum cephalosporins	25 (24,068)	27 (19,758)	15 (4,310)
Aminoglycosides	24 (24,514)	25 (20,094)	21 (4,420)
Piperacillin/ piperacillin/tazobactam	21 (21,529)	24 (17,741)	10 (3,788)
MDR per CDC definitions	20 (24,562)	22 (20,134)	11 (4,428)
Total Number of Isolates	24,562	20,134	4,428

CDC= Centers for Disease Control and Prevention; MDR= Multidrug resistant
Data are % non-susceptible (number of isolates tested)

Extended-spectrum cephalosporins category included ceftazidime and cefepime.
Fluoroquinolones category included levofloxacin and ciprofloxacin.
Aminoglycosides category included amikacin, gentamicin, and tobramycin.
Carbapenems category included imipenem, meropenem, and doripenem.
Piperacillins included piperacillin and piperacillin/tazobactam.
CDC MDR was defined as non-susceptibility to at least one agent in at least three of the following 5 categories: aminoclycosides, carbapenems, extended-spectrum cephalosporins, fluoroquinolones, and piperacillins.

Table 2. *Pseudomonas aeruginosa* Antibiotic Resistance Rates for Respiratory and Blood Cultures among Veterans Affairs Facilities Nationally by Culture Source from 2009 to 2013

	Source		
Antibiotic Category	Overall	Lung	Blood
Fluoroquinolones	33 (23,938)	34 (20.493)	28 (3,445)
Carbapenems	25 (21,176)	25 (18,089)	20.8 (3,087)
Extended-spectrum cephalosporins	25 (24,068)	25 (20,594)	21 (3,474)
Aminoglycosides	24 (24,514)	25 (20.988)	18 (3,526)
Piperacillins	21 (21,529)	22 (18,416)	18 (3,113)
MDR per CDC definitions	20 (24,562)	21 (21,031)	17 (3,531)
Total Number of Isolates	24,562	21,031	3,531

CDC= Centers for Disease Control and Prevention; MDR= Multidrug resistant
Data are % non-susceptible (number of isolates tested)

Extended-spectrum cephalosporins category included ceftazidime and cefepime.
Fluoroquinolones category included levofloxacin and ciprofloxacin.
Aminoglycosides category included amikacin, gentamicin, and tobramycin.
Carbapenems category included imipenem, meropenem, and doripenem.
Piperacillins included piperacillin and piperacillin/tazobactam.
CDC MDR was defined as non-susceptibility to at least one agent in at least three of the following 5 categories: aminoclycosides, carbapenems, extended-spectrum cephalosporins, fluoroquinolones, and piperacillins.

Figure 1. ***Pseudomonas aeruginosa*** **Antibiotic Resistance Among Veterans Affairs Inpatient Facilities by CDC Region**

AMG= Aminoglycosides; CDC= Centers for Disease Control and Prevention; E N Central= East North Central Region; E S Central= East South Central Region; ES Ceph= Extended-spectrum cephalosporin; FQ= Fluoroquinolone; MDR= Multidrug resistant; Mid Atlantic= Middle Atlantic Region; Mountain=Mountain Region; New England= New England Region; Pacific= Pacific Region; PIP= Piperacillins; S Atlantic= South Atlantic Region; W N Central= West North Central Region; W S Central= West South Central Region

Data are % non-susceptible (total number of isolates tested). Not every antibiotic category tested for every isolate tested.

Extended-spectrum cephalosporins category included ceftazidime and cefepime.
Fluoroquinolones category included levofloxacin and ciprofloxacin.
Aminoglycosides category included amikacin, gentamicin, and tobramycin.
Carbapenems category included imipenem, meropenem, and doripenem.
Piperacillins included piperacillin and piperacillin/tazobactam.
CDC MDR was defined as non-susceptibility to at least one agent in at least three of the following 5 categories: aminoclycosides, carbapenems, extended-spectrum cephalosporins, fluoroquinolones, and piperacillins.

Figure 2. ***Pseudomonas aeruginosa*** **Antibiotic Resistance Among Veterans Affairs Outpatient Facilities by CDC Region**

AMG= Aminoglycosides; CDC= Centers for Disease Control and Prevention; E N Central= East North Central Region; E S Central= East South Central Region; ES Ceph= Extended-spectrum cephalosporin; FQ= Fluoroquinolone; MDR= Multidrug resistant; Mid Atlantic= Middle Atlantic Region; Mountain=Mountain Region; New England= New England Region; Pacific= Pacific Region; PIP= Piperacillins; S Atlantic= South Atlantic Region; W N Central= West North Central Region; W S Central= West South Central Region

Data are % non-susceptible (total number of isolates tested). Not every antibiotic category tested for every isolate tested.

Extended-spectrum cephalosporins category included ceftazidime and cefepime.
Fluoroquinolones category included levofloxacin and ciprofloxacin.
Aminoglycosides category included amikacin, gentamicin, and tobramycin.
Carbapenems category included imipenem, meropenem, and doripenem.
Piperacillins included piperacillin and piperacillin/tazobactam.
CDC MDR was defined as non-susceptibility to at least one agent in at least three of the following 5 categories: aminoclycosides, carbapenems, extended-spectrum cephalosporins, fluoroquinolones, and piperacillins.