2021

National trends in hospital, long-term care and outpatient Acinetobacter baumannii resistance rates

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TITLE

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Keywords: *Acinetobacter baumannii;* carbapenem-resistance; multidrug-resistance (MDR), trends; Veterans Affairs

ABSTRACT

WORD COUNT: 277

Introduction: *Acinetobacter baumannii* is a top priority pathogen of the World Health Organization and the Centers for Disease Control due to antibiotic resistance.

Gap Statement: Trends in *A. baumannii* resistance rates that include community isolates are unknown.

Aim: Identify trends in *A. baumannii* resistance rates across the Veterans Affairs (VA) Healthcare System including isolates from patients treated in hospitals, long-term care facilities, and outpatient clinics nationally.

Methodology: We included *A. baumannii* clinical cultures collected from VA patients from 2010-2018. Cultures were categorized by location: VA medical center (VAMCs), long-term care (LTC) units (community living centers [CLCs]), or outpatient. We assessed carbapenem-resistance, multidrug-resistance (MDR), and extensive drug-resistance (XDR). Time trends were assessed with Joinpoint regression.

Results: We identified 19,376 *A. baumannii* cultures (53% VAMCs, 4% CLCs, 43% outpatient). Respiratory cultures were the most common source of carbapenem-resistant (43%), MDR (49%), and XDR (21%) isolates. Over the study period, the number of *A. baumannii* cultures decreased significantly in VAMCs (11.9% per year). In 2018, carbapenem resistance was 28% in VAMCs and 36% in CLCs, and only 6% in outpatient isolates, while MDR was 31% in VAMCs and 36% in CLCs, and only 8% in outpatient isolates. Carbapenem-resistant, MDR, and XDR *A. baumannii* isolates decreased significantly in VAMCs and outpatient clinics over time (VAMCs: by 4.9%, 7.2%, and 6.9%; outpatient: by 11.3%, 10.5%, 10.2% per year). Resistant phenotypes remained stable in CLCs.

Conclusion: In the VA nationally, prevalence of *A. baumannii* is decreasing, as is resistance. Carbapenem-resistant and MDR *A. baumannii* remain common in VAMCs and CLCs. The focus

of infection control and antibiotic stewardship efforts to prevent transmission of resistant *A. baumannii* should be in hospital and LTC settings.

INTRODUCTION

Acinetobacter baumannii is a major cause of nosocomial infections, including pneumonia, bloodstream, and urinary tract infections. *A. baumannii* infections typically occur among patients with substantial healthcare exposures, in particular, those who are in intensive care units, have prolonged lengths of stay, are on mechanical ventilation, have indwelling catheters, and are treated with broad-spectrum antibiotics.(1) Through a variety of mechanisms, *A. baumannii* can develop resistance to most antibiotic classes including fluoroquinolones, aminoglycosides, cephalosporins, carbapenems, and ampicillin-sulbactam.(1) Unfortunately, most *A. baumannii* isolates are resistant to many of these antibiotics, leading to multidrug-resistance (MDR), which are difficult to treat infections with limited treatment options (2) For resistant infections, carbapenems have become the treatment of choice, however the emergence of carbapenem-resistant *A. baumannii* has further narrowed treatment options. Due to their healthcare burden, high morbidity and mortality, and limited treatability, MDR and carbapenem-resistant *Acinetobacter* have been identified as top priority pathogens by the World Health Organization and the Centers for Disease control and Prevention (CDC).(3-5) The CDC has reported that each year in the United States there are at least 7,300 MDR *Acinetobacter* infections with 500 resultant deaths, and 8,500 carbapenem-resistant *Acinetobacter* infections with 700 resultant deaths among hospitalized patients.(4, 6)

While *A. baumannii* is primarily a healthcare-associated pathogen, there have been growing reports of patients with severe infections in the community setting without any prior health care exposure.(7-9) Risk factors for community-acquired infection include smoking, alcoholism, chronic obstructive pulmonary disease, diabetes mellitus, and renal disease.(1, 10) Community-acquired *A. baumannii* may be less drug-resistant than hospital-acquired strains, but community-acquired infections have been associated with increased mortality (odds ratio, 5.72; 95% confidence interval, 1.02–32).(11) Despite the growing clinical importance of *A. baumannii* in the

community, large scale surveillance of *A. baumannii* antibiotic resistance rates often do not include community isolates.(12-14) As such, the objective of this study was to identify trends in *A. baumannii* resistance rates across the Veterans Affairs (VA) Healthcare System including isolates from patients treated in hospitals, long-term care facilities, and outpatient clinics nationally.

METHODS

We conducted a retrospective longitudinal assessment of annual trends in *A. baumannii* resistance rates among clinical cultures. The study was approved by the Institutional Review Board (IRB) and the Research and Development (R&D) Committee of the Providence Veterans Affairs Medical Center prior to initiation.

Data sources.

We used national VA clinical and administrative data accessed through the VA Informatics and Computing Infrastructure (VINCI) for this study. We extracted data including: inpatient and long-term care admissions, outpatient visits, and microbiology results. We captured all microbiology results that were entered into the electronic medical record over the study period. Total annual VA inpatient admissions and outpatient visits were captured from the Veterans Health Administration Support Services Center.

Population.

We included all *A. baumannii* clinical cultures collected from VA patients (>18 years) in VA medical centers (VAMCs), long-term care units/ facilities (known as community living centers [CLCs]), and outpatient clinics from January 1, 2010 and December 31, 2018. We included cultures collected from all body sites, categorized into respiratory, blood, urine, skin and tissue, and cultures from other sources were grouped as “other”.

Measures.

We evaluated the annual count of *A. baumannii* clinical cultures collected and rate of cultures collected per 100 admissions for inpatients (VAMCs and CLCs) and per 100 visits for outpatients.

For evaluation of resistance, we included the first isolate per patient, per facility, per year.(15) We described the proportion of resistant isolates (number of resistant isolates divided by number of non-duplicate isolates tested) for each year. We evaluated antibiotic susceptibility to the following antibiotic classes: extended-spectrum cephalosporins, fluoroquinolones, aminoglycosides, carbapenems, piperacillin/tazobactam, and ampicillin/sulbactam. We used the minimum inhibitory concentrations (MICs) reported by the clinical laboratory performing the antimicrobial susceptibility testing to define antibiotic susceptibility based on Clinical and Laboratory Standards Institute (CLSI) breakpoints for susceptibility where available. Antibiotic susceptibility interpretations (S, I, or R) of the clinical laboratory performing the testing were used where MICs were not reported. Isolates were considered resistant to an antibiotic class if non-susceptibility to at least 1 drug in that class was identified.(4) We also evaluated MDR and extensive drug resistance (XDR).(6) MDR was defined as non-susceptibility to at least 1 drug in at least 3 of the antibiotic classes evaluated. XDR was defined as non-susceptibility to at least 1 drug in all six antibiotic classes.

Statistical analyses.

We used descriptive statistical analysis (including counts and percentages) to characterize the data overall and by healthcare setting (VAMC, CLC, outpatient). We assessed time trends with Joinpoint regression to calculate average annual percent changes (AAPC) and 95% confidence intervals (CI). Significance was set at $p<0.05$.

RESULTS

Over the 9-year study period, 19,376 *A. baumannii* cultures (53% VAMCs, 4% CLCs, 43% outpatient) were identified. Overall, the number of *A. baumannii* cultures decreased from 2,778 to 1,684 between 2010 to 2018. Figure 1 presents the trends in the crude counts of cultures collected and the trends in the rate of *A. baumannii* cultures collected per 100 admissions/visits. In VAMCs, the crude number of *A. baumannii* cultures collected decreased significantly by 11.9% per year (95% CI -13.6% to -10.3%; Figure 1, Supplemental Table 1). In CLCs, the number of *A. baumannii* cultures decreased significantly by 14.9% per year (95% CI -14.1% to -10.6%). The number of *A. baumannii* cultures collected in outpatient clinics remained stable over the study period. For trends in rates of *A. baumannii* cultures collected per 100 admissions, similar results were observed in VAMCs and CLCs as those found for crude culture counts in those settings. However, in contrast to crude culture count findings in the outpatient setting, the rate of cultures collected per 100 visits in outpatient clinics decreased significantly by 3.2% per year (95% CI -6.1% to -0.2%).

Overall, respiratory cultures were the most common source of carbapenem-resistant (43%), MDR (49%), and XDR (21%) isolates (Figure 2), which was also observed in VAMCs (carbapenem-resistant 46% and MDR 53%) and in CLCs (carbapenem-resistant 54% and MDR 56%; Supplemental Table 2). Blood cultures were the most common sources of carbapenem-resistant (19%) and MDR (17%) isolates in outpatient clinics.

Antibiotic resistance for *A. baumannii* decreased significantly over the study period. In all settings, carbapenem resistance decreased significantly by 8.6% per year (95% CI -10.8% to -6.4%, Figure 3, Supplemental Table 3). In VAMCs, carbapenem resistance in *A. baumannii* decreased by 4.9% per year (95% CI -7.0% to -2.7%) from 39% in 2010 to 28% in 2018. In outpatient clinics, carbapenem resistance in *A. baumannii* decreased by 11.3% per year (95% CI -17.2% to -5.0%)

from 12% in 2010 to 6% in 2018. Carbapenem resistance remained stable in CLCs (28% in 2010 and 36% in 2018).

In all settings, MDR in *A. baumannii* decreased by 10.2% per year (95% CI -12.7% to -7.7%; 37% in 2010 and 18% in 2018) and XDR decreased by 9.4% per year (95% CI -14.7% to -3.8%, 37% in 2010 and 18% in 2018, Figure 3). In VAMCs, MDR and XDR rates decreased by 7.2% per year 95% (CI -9.6% to -4.7%) and 6.9% per year (95% CI -11.9% to -1.6%), respectively. Similarly, in outpatient clinics, MDR decreased by 10.5% per year (95% CI -14.5% to -6.3%) and XDR by 10.2% per year (95% CI -17.0% to -2.9%). MDR and XDR isolates remained stable in CLCs (MDR 44% in 2010 and 36% in 2018; XDR 14% in 2010 and 22% in 2018).

DISCUSSION

Our study is among the first large scale study of *A. baumannii* resistance trends to include isolates collected from all healthcare settings including hospitals, long-term care, and outpatient clinics. We observed significant decreases in *A. baumannii* clinical cultures among VA inpatient populations over our recent 9-year study period. We also observed significant decreases in *A. baumannii* resistance, including MDR (-10.2%), XDR (-9.4%), carbapenem-resistant (-8.6%) phenotypes. Despite these improvements, *A. baumannii* resistance rates remained high in 2018, particularly in inpatient settings (VAMCs: carbapenem-resistant 28% and MDR 31%; CLCs: carbapenem-resistant 36% and MDR 36%), which present challenges to effective treatment.

The decreasing trends in the number of *A. baumannii* clinical cultures we observed in inpatients over our study period from 2010 to 2018 are supported by prior longitudinal analyses.(2, 12) Surveillance of routine clinical respiratory and bloodstream specimens from 217 hospitals in the United States (US) demonstrated a decrease in *A. baumannii* specimens from 2003 to 2012.(2)

Between 2003-2005, 16,250 *A. baumannii* specimens (41.3%) were isolated, as compared to only 9,430 (24.0%) between 2009-2012.(2)

We assessed crude counts of number of positive *A. baumannii* isolates collected in each setting and also the rate of positive *A. baumannii* isolates collected per 100 admissions/visits, accounting for changes in number of inpatient stays/outpatient visits year to year. The crude number of clinical cultures from inpatient settings (both VAMCs and CLCs) decreased, while the number collected from outpatient settings remained stable. The rate of *A. baumannii* cultures collected per 100 admissions/visits decreased in all settings, including outpatient clinics. There is limited surveillance data which include *A. baumannii* isolates from outpatient settings. However, there are reports that the community-acquired *A. baumannii* infections may be increasing gradually in other populations.(16)

In VAMCs, we found that resistance rates were decreasing, which is supported by previous work.(12, 13, 17, 18) Of 19,325 *Acinetobacter* species (spp.) isolates from 411 hospitals in the US from 2013-2017, 37% were carbapenem-nonsusceptible and 48% were MDR.(12) Rates of carbapenem-nonsusceptible and MDR *Acinetobacter spp.* isolates collected per 100 hospital admissions decreased over their 5 year study period.(12) Additionally, the CDC's most recent Antibiotic Resistance Threats report demonstrated a 33% reduction in annual estimated carbapenem-resistant *A. baumannii* infections in US hospitals from 2013 to 2019.(4) In 2019, the CDC estimated there were 8,500 infections due to carbapenem-resistant *A. baumannii* occurring annually in US hospitals as compared to the estimated 11,700 annual carbapenem-resistant infections from the 2013 report.(4, 6) The CDC recognized dedicated infection control and prevention and antibiotic stewardship efforts, particularly in US hospitals, as important factors contributing to decreased rates of drug-resistant infections.(4)

We too attribute the overall decreased *A. baumannii* resistance patterns, including significant reductions in carbapenem-resistant, MRR, and XDR phenotypes, we observed to robust infection control and antimicrobial stewardship initiatives that are instituted in VAMCs nationally.(19-21) In 2007, the VA implemented a methicillin-resistant *Staphylococcus aureus* (MRSA) infection control bundle among all VA medical centers, and previous work has shown that this initiative may have led to reductions in gram-negative bacteria through expanded infection control programs and resources.(22) In 2011, the VA established the National Antimicrobial Stewardship Task Force (ASTF) and in 2014 the VA required all of its hospitals to have antibiotic stewardship programs.(23) Previous work has demonstrated an increase in antimicrobial stewardship in VAMCs over the study period.(24) Previous work has also shown that multidisciplinary antimicrobial stewardship initiatives reduce drug-resistant infections and colonization by encouraging judicious antibiotic prescribing practices.(25-27) A previous meta-analysis found that antimicrobial stewardship programs reduced infections and colonization with MDR gram-negative bacteria by 51%.(25) Antimicrobial stewardship programs were most effective at reducing the incidence of antibiotic resistant infections when implemented alongside infection control practices.(25, 28)

We observed decreased rates of resistant *A. baumannii* phenotypes in outpatient VA clinics. Antibiotic stewardship and infection control programs are generally not as robust in outpatient clinics as compared to inpatient settings, however, outpatient antimicrobial stewardship is becoming increasingly common which may partly explain our findings.(29) Moreover, the VA is an integrated healthcare system with coordinated care across settings, and therefore, VAMCs and outpatient clinics do not function in isolation. While antimicrobial stewardship efforts mainly occur in VAMCs, the benefits of stewardship may extend to the outpatient setting through shared patients and providers, thus conferring improvements in resistance across clinical settings.

Despite improvements, more action is needed, especially in hospital and long-term care settings. In CLCs, the proportions of carbapenem-resistant, MDR, and XRD isolates remained stable over our study period. In 2018, about 1/3 of isolates in VAMCs and CLCs were MDR (31% VAMCs and 36% CLCs) and about 1/3 were carbapenem-resistant (28% VAMCs and 36% CLCs), as compared to only 8% and 6%, respectively in outpatient clinics. Similarly, prior work assessed isolates from two hospitals and also community isolates, of which 37% of the hospital isolates were MDR phenotypes, while none of the community isolates were MDR.(30) Among 598 carbapenem-nonsusceptible *A. baumannii* cases from hospital samples, nearly all (99%) had healthcare exposure in the prior year, which was most commonly a stay at an acute care hospital or long-term care facility.(31) Similar to previous work, our results also support recommendations to focus on preventing *A. baumannii* transmission in hospital and long-term care settings.(31, 32)

The high rates of resistant *A. baumannii* phenotypes in our study are concerning as MDR and carbapenem-resistant infections are a challenge to treat and associated with poor outcomes.(33) As traditional treatment options are limited and often associated with high toxicity, newer agents are becoming increasingly important in the treatment of serious resistant *A. baumannii* infections.(34) This may be especially important for the treatment of pneumonia in the VA, as we found respiratory cultures were the most common source of resistant phenotypes. These results have been also demonstrated outside of the VA, with respiratory cultures also being the most common source of carbapenem-nonsusceptible and MDR *Acinetobacter spp.* among non-VA hospitalized patients in the US.(12)

Limitations.

There are limitations inherent in our work. Clinical symptoms and signs were not assessed in this study, so we did not discern between colonization and actual clinical infection. Nevertheless, changes in numbers of clinical cultures and resistance rates in *A. baumannii* are important data

that can guide infection control protocols and empiric antibiotic practices. An inherent weakness of this retrospective study is that we had to rely on the bacterial identification and antimicrobial susceptibility testing methods used by the clinical laboratories processing the isolates. Bacterial identification and antimicrobial susceptibility testing methods are not uniform across laboratories nationally in the VA Healthcare system; various centers may use different systems to identify bacteria and determine antibiotic susceptibility which can influence calculated resistance rates. However, we used the reported MIC to determine resistance when available, otherwise we used the interpretations of the clinical laboratory handling the culture. Additionally, while our 9-year study period is a strength, resistance testing may not have been uniform across all study years. There may be some misclassification of culture collection site as it is a free text field, and can be entered as a non-specific site (e.g. fluid). Non-specific culture sites and culture sites with low count were therefore categorized as “other”. We only included cultures that were captured by the VA electronic medical record, and therefore did not include cultures that were obtained at outside laboratories and not entered into the VA system. The generalizability of our results is limited to the VA population, which is known to be older and more male than the general US population. Finally, as the objective of our resistance surveillance study was to quantify trends in resistance of *A. baumannii* isolates, we did not evaluate clinical, epidemiological, or treatment characteristics of the patients with these positive cultures. Additionally, we did not assess adherence to infection control, administration policies, or antibiotic stewardship programs that may have been implemented over the study period. These should be further explored, to determine their effect on microbial epidemiology.

Conclusion.

We observed significant decreases in *A. baumannii* clinical cultures among VA inpatient populations and significant decreases in *A. baumannii* resistance, including MDR, XDR, and carbapenem-resistant isolates, in inpatients and outpatients over our recent 9-year study period.

In 2018, MDR and carbapenem-resistant *A. baumannii* remained common, especially in inpatient settings, which presents challenges to effective treatment. Despite improvements, our results highlight the importance of continued infection control and antimicrobial stewardship efforts focused in inpatient and long-term care settings. Future work is warranted to quantify the epidemiology of *A. baumannii* in different clinical settings and changes in the epidemiology over time, including risk factors of *A. baumannii*, as well as treatment and other factors that affect clinical outcomes of *A. baumannii*.

Author and contributions:

Conception and design of the study: HA, ARC, KL

Data generation: HA, ARC, VL

Analysis and interpretation of the data: HA, ARC, EO, VL, KL

Preparation or critical revision of the manuscript: HA, ARC, EO, VL, KL

Conflicts of interest:

Haley Appaneal has received research funding from Shionogi.

Aisling Caffrey has received research funding from Pfizer, Merck (Cubist), and Shionogi.

Kerry LaPlante has received research funding or acted as a scientific advisor for Merck, Parateck, Pfizer, Spero, and Shionogi.

No other financial disclosures.

Funding information:

This work was funded in part by Shionogi, Inc.

Acknowledgements:

The views expressed are those of the authors and do not necessarily reflect the position or policy of the United States Department of Veterans Affairs. This material is based upon work supported, in part, by the Office of Research and Development, Department of Veterans Affairs.

Ethics approval:

The study was approved by the Institutional Review Board (IRB) and the Research and Development (R&D) Committee of the Providence Veterans Affairs Medical Center prior to initiation. This research was conducted with a waiver of informed consent from the Providence VA Medical Center IRB.

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Figure 1. Overall trends in *A. baumanii* culture collection, by healthcare setting (VAMC, CLC, Outpatient)

VAMC= Veterans Affairs Medical Centers; CLC= Community Living Centers; Outpatient= Outpatient Clinics

The Joinpoint Regression Program was used to calculate average annual percent change (AAPC) and 95% confidence intervals (95% CI).

* indicates p-value <0.05.

Figure 2. Frequency of A*cinetobacter baumanii* resistant phenotypes, by culture site

Carbapenem-resistant (CARB-R) was defined as resistance to imipenem, meropenem, or doripenem.

Multidrug-resistant (MDR) was defined as resistance to at least 1 drug in at least 3 antibiotic classes: extended-spectrum cephalosporins, fluoroquinolones, aminoglycosides, carbapenems, piperacillin/tazobactam, and ampicillin/sulbactam.

Extensively drug resistant (XDR) was defined as resistance to at least 1 drug in six antibiotic classes: extended-spectrum cephalosporins, fluoroquinolones, aminoglycosides, carbapenems, piperacillin/tazobactam, ampicillin/sulbactam, polymyxins, sulfamethoxazole/trimethoprim, tetracyclines and tigecycline.

Figure 3. Trends in A*cinetobacter baumanii* resistant phenotypes, by healthcare setting (VAMC, CLC, Outpatient)

VAMC= Veterans Affairs Medical Centers; CLC= Community Living Centers; Outpatient= Outpatient Clinics

* indicates p-value <0.05 for time trend.

Carbapenem-resistant (CARB-R) was defined as resistance to imipenem, meropenem, or doripenem.

Multidrug-resistant (MDR) was defined as resistance to at least 1 drug in at least 3 antibiotic classes: extended-spectrum cephalosporins, fluoroquinolones, aminoglycosides, carbapenems, piperacillin/tazobactam, and ampicillin/sulbactam.

Extensively drug resistant (XDR) was defined as resistance to at least 1 drug in six antibiotic classes: extended-spectrum cephalosporins, fluoroquinolones, aminoglycosides, carbapenems, piperacillin/tazobactam, ampicillin/sulbactam, polymyxins, sulfamethoxazole/trimethoprim, tetracyclines and tigecycline