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Epidemiology and Clinical Outcomes Associated with Extensively-drug Resistant (XDR) *Acinetobacter* in U.S. Veterans Affairs (VA) Medical Centers

Margaret A. Fitzpatrick, MD, MS,

Department of Veterans Affairs, Center of Innovation for Complex Chronic Healthcare, Edward Hines, Jr. VA Hospital, Hines, IL, USA; Department of Medicine, Division of Infectious Diseases, Loyola University Chicago Stritch School of Medicine, Maywood, IL, USA, 5000 S. Fifth Ave., Hines, IL 60141

Katie J. Suda, PharmD, MS

Department of Veterans Affairs, Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System, Pittsburgh, PA, USA; Department of Medicine, Division of General Internal Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Linda Poggensee, MS, Amanda Vivo, MPH, Marissa Wirth, MPH, Geneva Wilson, PhD

Department of Veterans Affairs, Center of Innovation for Complex Chronic Healthcare, Edward Hines, Jr. VA Hospital, Hines, IL, USA

Martin Evans, MD,

VHA MRSA/MDRO Program Office, the National Infectious Diseases Service, Patient Care Services, VA Central Office and the Lexington VA Medical Center, Lexington, KY, USA; Department of Internal Medicine, University of Kentucky School of Medicine, Lexington, KY, USA

Charlesnika T. Evans, PhD, MPH

Department of Veterans Affairs, Center of Innovation for Complex Chronic Healthcare, Edward Hines, Jr. VA Hospital, Hines, IL, USA; 5Center for Health Services and Outcomes Research, Department of Preventive Medicine Institute for Public Health and Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Abstract

Objective: Although infections caused by *Acinetobacter baumannii* (AB) are often healthcare-acquired, difficult to treat, and associated with high mortality, epidemiologic data for this organism are limited. This study's aim was to describe epidemiology, clinical characteristics, and outcomes for patients with XDRAB.

Design: Retrospective cohort study

Setting: Department of Veterans Affairs Medical Centers (VAMCs)

Corresponding Author: Phone: 708-202-4444, Margaret.fitzpatrick@va.gov.

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Participants: Patients with XDRAB cultures (defined as non-susceptible to at least 1 agent in all but 2 or fewer classes) at VAMCs between 2012–2018.

Methods: Microbiology and clinical data was extracted from national VA datasets. Descriptive statistics summarized patient characteristics and outcomes, and bivariate analyses compared outcomes by culture source.

Results: Among 11,546 patients with 15,364 *A. baumannii* cultures, 408 (3.5%) patients had 667 (4.3%) XDRAB cultures. Patients with XDRAB were older [mean age (SD)=68 (12.2) years] with median (IQR) Charlson index 3 (1–5). Respiratory (n=244, 36.6%) and urine (n=187, 28%) were the most frequent sources; the greatest proportion of patients were from the South (n=162, 39.7%). Most patients had antibiotic exposures (n=362, 88.7%) and hospital or long-term care admissions (n=331, 81%) in the prior 90 days. Polymyxins, tigecycline, and minocycline demonstrated the highest susceptibility. 30-day (n=96, 23.5%) and one-year (n=199, 48.8%) mortality were high, with significantly higher mortality in patients with blood cultures.

Conclusions: The proportion of AB in the VA that was XDR was low, but treatment options were extremely limited and clinical outcomes were poor. Prevention of healthcare associated XDRAB infection should remain a priority, and novel antibiotics for XDRAB treatment are urgently needed.

Introduction:

Members of the *Acinetobacter baumannii* complex (subsequently referred to as *A. baumannii*) can cause severe healthcare-associated infections such as hospital-acquired bacterial pneumonia/ventilator-associated pneumonia (HABP/VAP) and bloodstream infections (BSIs). In 2017, carbapenem-resistant *A. baumannii* caused an estimated 8,500 infections in hospitalized patients and 700 deaths in the United States.¹ Although incidence is lower than for other healthcare-associated pathogens, *A. baumannii* infections are frequently multidrug resistant (MDR), making them difficult to treat and associated with high mortality.^{2,3} Increased mortality from MDR *A. baumannii* (MDRAB) infections has been associated with inappropriate antibiotic treatment due to multi-drug resistance.^{4,5}

Extensively-drug resistant (XDR) *A. baumannii* (XDRAB) are a subset of MDRAB that have been categorized as non-susceptible to at least one agent in all but two or fewer antimicrobial classes.⁶ From 2015–2017, the Centers for Disease Control and Prevention's (CDC) National Healthcare Safety Network (NHSN) reported that 46% of *Acinetobacter* spp. causing central line-associated BSI in hospital intensive care units (ICUs) and 76% in long-term acute care hospitals (LTACHs) were MDR.⁷ Prior large, multicenter epidemiologic studies of *A. baumannii* have focused on carbapenem-resistant *A. baumannii* without specifically characterizing XDRAB.^{2,7,13} Although carbapenem-resistance in *Acinetobacter* is often observed in association with resistance to multiple antibiotic classes, not all carbapenem-resistant *A. baumannii* are XDR; therefore, important epidemiologic and clinical differences may exist for the subgroup of patients with XDRAB. Existing data on XDRAB comes largely from smaller, single center studies conducted outside the U.S.^{8–10} In this national cohort study, we used data from U.S. Department of

Veterans Affairs (VA) hospitals to describe the epidemiology, clinical characteristics, and outcomes for patients with XDRAB in the VA.

Methods:

This was a retrospective cohort study including microbiology and clinical data from adult patients with utilization at any VA medical center (VAMC) between January 1, 2012 and December 31, 2018. Microbiology, clinical, and facility data were obtained from the VA Corporate Data Warehouse (CDW), which is a national repository including clinical and administrative data from Veterans Health Administration (VHA). Data are stored in a relational database and are updated on a continual basis. CDW datasets were used to collect data on patient demographics, Charlson comorbidity index¹¹, healthcare utilization, microbiologic data, and medication exposures. VA uses the Rural-Urban Commuting Areas system to classify VAMCs into urban vs. rural.¹² Urban VAMCs are in census tracts with at least 30% of the population residing in an urbanized area as defined by the U.S. Census Bureau. Rural VAMCs are in areas not defined as urban. The institutional review board at the Edward Hines, Jr. VA Hospital approved this study.

All bacterial cultures collected from patients during the study period that grew XDRAB were included. Performance and reporting of bacterial speciation and antibiotic susceptibility testing was performed by each VA laboratory according to their own protocol. Isolates were classified as XDR if they were non-susceptible to at least one agent in all but two or fewer antimicrobial classes active against *Acinetobacter*.⁶ To validate the XDR classification from the CDW data, medical records were reviewed for a stratified sample of 63 inpatient cultures (17 blood, 21 urine, and 25 respiratory) that had an associated ICD10 code for sepsis, urinary tract infection, or pneumonia during the admission. Agreement between XDRAB categorization for these cultures using CDW data and medical record review was 95%. Discrepancies were due to antibiotic susceptibilities that had been manually entered as text into Microbiology culture reports. Multiple cultures from the same patient within 30 days were removed. Descriptive statistics were used to summarize patient demographics, clinical characteristics, and prior healthcare and antibiotic exposures as well as hospital characteristics. For the analysis of clinical outcomes, we analyzed data for all patients together as well as patients grouped by culture source. If one patient had XDRAB cultures > 30 days apart from multiple sources over the course of the study, a hierarchical approach was taken. For any patient with XDRAB isolated from blood, outcomes were analyzed with the source as blood. For patients without blood isolates but positive respiratory isolates, outcomes were analyzed with the source as respiratory. For patients without blood or respiratory isolates but positive urine isolates, outcomes were analyzed with the source as urine. Finally, for patients without blood, respiratory, or urine isolates, outcomes were analyzed with the source as other. Fisher's Exact test and Wilcoxon rank-sum test were used to assess differences in clinical outcomes by culture source. Bonferroni correction for multiple comparisons was used, with $p < 0.008$ considered significant. Statistical analyses were carried out using SAS, version 9.4 (SAS Institute) and Stata, version 12.1 (Stata Corp LP).

Results:

Out of 11,546 unique patients with 15,364 cultures that grew *A. baumannii* during the study period, 408 (3.5%) patients had 667 (4.3%) cultures that grew XDRAB. Patient demographics, clinical characteristics, and culture characteristics are in Table 1. Most patients were older men, and many had comorbidities such as diabetes (n=165, 40.4%) and chronic kidney disease (n=162, 37.9%). Most cultures were obtained from inpatients (n=468, 70.2%), with the greatest proportion of isolates coming from the respiratory tract (n=244, 36.6%) followed by urine (n=187, 28%). The proportion of all XDRAB isolated during the study period that occurred each study year declined from 33.7% in 2012 to 7.5% in 2018.

Most patients (n=362, 88.7%) had antibiotic exposures in the 90 days prior to their XDRAB culture, with vancomycin (n=289, 70.8%) and extended spectrum penicillins (n=128, 55.9%) being the most common. Most patients (n=331, 81.1%) also had a hospital or long-term care admission in the prior 90 days, with nearly half (45.1%) having an ICU admission and nearly a third (28.3%) having had mechanical ventilation in the prior 90 days. Antibiotic susceptibilities of the XDRAB isolates were variable (Figure 1). Polymyxins (n=128/133, 96.2%), tigecycline (n=72/106, 67.9%), and minocycline (n=52/121, 43.0%) demonstrated the highest susceptibility. By contrast, susceptibilities to anti-Pseudomonal fluoroquinolones and extended spectrum penicillins were quite low at 0.2% and 0.3%, respectively. The geographic distribution of VAMCs with patients with XDRAB is shown in Figure 2. Overall, XDRAB cultures were identified from patients at 41 VAMCs in 23 states and Puerto Rico. The Southern region (which included Puerto Rico) had the largest proportion of patients with XDRAB (n=162, 39.7%), while the Midwest had the smallest (n=55, 13.5%). Almost all patients were cared for at urban VAMCs (n=404, 99%).

Clinical outcomes for patients with XDRAB are shown in Table 2. Almost a quarter of patients died within 30 days following their XDRAB culture. When analyzed by culture source, all mortality outcomes were significantly more frequent in patients with XDRAB from blood cultures compared to respiratory, urine, and other culture sources. Hospital readmission within 90 days and length of stay (LOS) were calculated for the subset of patients whose cultures were obtained from inpatient or long-term care facility (LTCF) settings. Median post-culture LOS was high at 31 days. Neither outcome differed significantly by culture source. When patients with cultures obtained from LTCF settings were excluded, post-culture LOS decreased for urine [median (IQR) of 22 (8–49) days vs 32 (9–77) days] and other [12 (6–55) days vs. 19 (17–110) days] culture sources but remained relatively unchanged for blood [16 (9–32) days vs. 18 (11–38) days] and respiratory [20 (8–42) days vs. 21 (8–52) days] culture sources.

Discussion:

National CDC surveillance data has shown that overall incidence of MDRO infections remains low compared to other MDROs²; however, MDRO can cause severe, nosocomial infections with higher attributable mortality and fewer antibiotic treatment options compared to many other MDROs.^{4,13} Therefore, accurate and up-to-date characterization of the

epidemiology and outcomes of diverse patient populations with MDRAB and XDRAB is critical to inform local and national surveillance, to guide infection prevention and antibiotic stewardship efforts, and to assist clinicians in management of these infections.

In this national cohort study of Veterans with XDRAB cared for at over 40 different geographically diverse VAMCs, we found an overall low prevalence of XDR (3.5%) among patients with *A. baumannii*. Furthermore, the proportion of all XDRAB cultures that were isolated each study year decreased over time, from a high of 33.7% in 2012 to 7.5% in 2018. This decline is consistent with NHSN data on healthcare-associated infections, where the percentage of *A. baumannii* that were carbapenem-resistant decreased from 58% in 2011¹⁴ to 39% between 2015–2017⁷, as well as data recently published from a national cohort of U.S. hospitals where the incidence of carbapenem-resistant *A. baumannii* declined between 2012–2017 from 3.33 to 2.47 per 10,000 hospitalizations.¹⁵ Similar to many healthcare systems, the VA implemented various infection prevention and antimicrobial stewardship interventions during our study period that likely contributed to declines in multiple MDRO types, including MDRAB.¹⁶ Declines may also be due to changes in factors specific to the virulence and spread of *Acinetobacter*.

Most patients in our study were older, with chronic comorbidities and recent healthcare and antibiotic exposures, and most cultures were collected from the respiratory or urinary tract. Recent prior healthcare and antibiotic exposures have been shown in multiple other studies to correlate strongly with an increased risk of MDRAB.^{2,3} Furthermore, almost all XDRAB cultures were collected from patients at urban VAMCs, with the South having the greatest proportion of patients. Geographic variability in the epidemiology of MDRAB and other MDROs has been described, and may stem from local spread of resistant clonal isolates, regional differences in antimicrobial stewardship, variability in infection control practices, or other factors.^{2,17} Taken collectively, this epidemiologic data informs clinicians and infection control practitioners to have heightened suspicion for XDRAB in patients with prior healthcare and antibiotic exposures, particularly if they have respiratory or urinary tract infections and are being cared for at urban medical centers.

Another interesting finding from our study was that two of the most common prior antibiotic exposures in patients with XDRAB were extended spectrum penicillins and anti-Pseudomonal fluoroquinolones. Although we did not report on treatments, one possibility for the high exposure to these classes is because they are common empiric antibiotics prescribed for infections frequently caused by XDRAB (e.g., sepsis, nosocomial pneumonia, complicated urinary tract infections). Unfortunately, our data showed almost negligible susceptibility of XDRAB isolates to these antibiotic classes, highlighting the low likelihood that common empiric antibiotic regimens are appropriate for patients with XDRAB infections. Multiple studies have identified associations between delays in appropriate antibiotic treatment and increased mortality in patients with MDRAB,^{4,5} which may partly account for the poor clinical outcomes we observed. Many new antibiotics (e.g., ceftazidime/avibactam, ceftolozane/tazobactam, meropenem/vaborbactam, imipenem/relebactam) have fewer toxicities compared to existing treatments for MDR Gram-negative bacteria but lack activity against MDRAB,^{18,19} often leaving polymyxins, tigecycline, and minocycline as the only treatment options. These drugs have substantial limitations,

including high rates of adverse reactions and limited efficacy for certain infection sites. Thus, additional studies are needed to determine the effectiveness and outcomes of various treatment regimens for XDRAB, and drug development pipelines for novel antibiotics with activity against XDRAB should be supported.²⁰

Finally, clinically outcomes in patients with XDRAB were generally poor. Almost a quarter of patients died within 30 days following the positive culture, and almost half of patients had died within a year after a positive culture. Among inpatients and those in LTCFs, a quarter were re-hospitalized within 90-days, and median post-culture LOS was a month. As anticipated, outcomes were worse for patients with positive blood and/or respiratory cultures compared to urine or other cultures, which may indicate a greater likelihood that XDRAB cultured from non-blood, non-respiratory sites reflects colonization rather than true infection. Isolation of XDRAB has been associated with high in-hospital and 30-day mortality in prior studies.^{8–10} Although some of this association is explained by the propensity of *Acinetobacter* to infect hospitalized, medically complex patients with high baseline risk for mortality, prior studies have shown substantial attributable mortality from MDRAB infections specifically.^{4,12}

Our study had several important limitations. First, it was retrospective and observational, and, consistent with our aim to provide a descriptive analysis, did not include a comparator group of patients with susceptible *Acinetobacter* cultures. Second, our study was conducted using VA data and may not be fully representative of XDRAB epidemiology in non-VA populations. Third, although the national VA databases used in this study were necessary to amass a large and diverse cohort with a low prevalence MDRO such as XDRAB, they lacked key information regarding presence of indwelling devices and variables needed to differentiate colonized vs infected patients from those with true infection. We hypothesized that patients with XDRAB isolated in the blood or respiratory tract were may be more likely to have true infection than those with urine or other cultures, and our observation of worse outcomes for these patients supports this hypothesis. However, many of the respiratory tract cultures may also have been colonization, and patients with XDRAB blood and respiratory tract cultures could also have been more medically complex and had greater healthcare and antibiotic exposures. Finally, the identification and reporting of bacterial susceptibilities by individual VA microbiology labs is expected to follow Clinical and Laboratory Standards Institutes guidelines, but may have varied during the study period, leading to limitations in the accuracy of XDRAB identification and aggregated antibiotic susceptibilities reported.

In conclusion, the proportion of *A. baumannii* isolates in the VA that were XDR was overall low (3.5%), with substantial declines noted between 2012–2018. XDRAB was more common among patients with recent healthcare and antibiotic exposures who were cared for at urban VAMCs, was associated with poor clinical outcomes, and demonstrated extremely limited antibiotic susceptibilities. Therefore, providers should continue to suspect XDRAB infection in patients with these epidemiologic risks and should continue to monitor and disseminate local surveillance and antibiogram data for this pathogen.

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Figure 1. Antibiotic susceptibility of XDR *Acinetobacter* isolates

Percent of XDRAB isolates testing susceptible to key antibiotics. Individual antibiotics are grouped into relevant classes by color.

Figure 2. Geographic distribution of XDR *Acinetobacter*

Geographic distribution of patients with XDRAB cultures in VAMCs. Circle size corresponds to the number of patients with XDRAB cultures at VAMCs in that state or territory (Puerto Rico). Varying color shades indicate U.S. Census Bureau regions.

Table 1.

Patient demographics, clinical and culture characteristics, and exposures.

Patient characteristics (n=408)	Number (%)^a
Demographics	
Age, years, mean (SD)	68.1 (12.2)
Sex, female	6 (1.5)
Comorbidities	
Charlson comorbidity index, median (IQR)	3 (1–5)
Chronic kidney disease	162 (39.7)
Chronic liver disease	36 (8.8)
HIV/AIDS	5 (1.2)
Malignancy or tumor	49 (12.0)
CHF	90 (22.1)
Diabetes	165 (40.4)
Cerebrovascular disease	60 (14.7)
Peripheral vascular disease	84 (20.6)
Healthcare exposures in past 90 days	
Hospital admission	331 (81.1)
LTCF or rehabilitation stay	32 (7.8)
Surgery	57 (14.0)
ICU admission	184 (45.1)
Mechanical ventilation	118 (28.9)
Antibiotic exposures in past 90 days	
Any antibiotic	362 (88.7)
Penicillins	97 (23.8)
Extended spectrum penicillins	228 (55.9)
1 st /2 nd gen cephalosporins	70 (17.1)
3 rd /4 th gen cephalosporins	171 (41.9)
Carbapenems	78 (19.1)
Tetracyclines	74 (18.1)
Aminoglycosides	79 (19.3)
Fluoroquinolones	216 (52.9)
Vancomycin	289 (70.8)
Culture characteristics (n=667)	Number (%)^a
Care setting where culture was obtained	
Inpatient	468 (70.2)
Outpatient	114 (17.1)
Long-term care	85 (12.7)
Culture source	
Blood	49 (7.4)
Urine	187 (28.0)

Respiratory	244 (36.6)
Other	187 (28.0)
Culture year	
2012	225 (33.7)
2013	126 (18.9)
2014	81 (12.1)
2015	79 (11.8)
2016	48 (7.2)
2017	58 (8.7)
2018	50 (7.5)

^aData reported are number (%) unless otherwise indicated

SD, standard deviation; IQR, interquartile range; HIV/AIDS, human immunodeficiency virus/acquired immune deficiency syndrome; CHF, congestive heart failure; LTCF, long-term care facility; ICU, intensive care unit

Table 2.

Clinical outcomes in patients with XDRA.

	Number (%)					
Outcome^a	Total	Blood (n=34)	Respiratory (n=140)	Urine (n=116)	Other (n=118)	p-value
In-hospital mortality (n=335)	92 (24.5)	15 (44.1)	51 (36.4)	11 (9.5)	15 (12.7)	<0.01
30-day mortality (n=408)	96 (23.5)	20 (58.9)	54 (38.6)	7 (6.0)	15 (12.7)	<0.01
1-year mortality (n=408)	199 (48.8)	25 (73.5)	98 (70.0)	39 (33.6)	37 (31.4)	<0.01
Outcome^b	Total	Blood (n=30)	Respiratory (n=133)	Urine (n=77)	Other (n=95)	p-value
90-day hospital readmission (n=553)	86 (25.7)	5 (16.7)	30 (22.6)	19 (24.7)	32 (33.7)	0.16
Post-culture LOS, days, median (IQR) ^b	31 (0–128)	18 (11–38)	21 (8–52)	32 (9–77)	19 (7–110)	NS ^c

LOS, length of stay; IQR, interquartile range

^aThese outcomes are reported at the patient level. In-hospital mortality is reported for the subset of patients with unique cultures obtained from inpatient or LTCF settings.

^bThese outcomes are reported at the unique culture level and were calculated for the subset of cultures obtained in inpatient or LTCF settings. Post-culture LOS was summed for all unique hospital and LTCF admissions.

^cP-values were calculated for each individual comparison and were all non-significant with p>0.008.