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Concise Communication

Carbapenem-resistant *Enterobacteriaceae* epidemiology in Veterans' Affairs medical centers varies by facility characteristics

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Abstract

This is an epidemiological study of carbapenem-resistant *Enterobacteriaceae* (CRE) in Veterans' Affairs medical centers (VAMCs). In 2017, almost 75% of VAMCs had at least 1 CRE case. We observed substantial geographic variability, with more cases in urban, complex facilities. This supports the benefit of tailoring infection control strategies to facility characteristics.

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Carbapenem-resistant *Enterobacteriaceae* (CRE) and, in particular, carbapenemase-producing (CP-) CRE, are a growing concern due to their multidrug-resistance and propensity to spread within healthcare facilities.[1] The Centers for Disease Control and Prevention has designated CRE an 'urgent threat'[2] due to an estimated incidence rate of 2.93 per 100,000 population, limited treatment options,[2] and a 40%–50% mortality rate.[1] Aggressive containment strategies could prevent 1,600 cases of CRE in 1 state over a 3-year period.[2] However, little research has been conducted looking at facility-level risk factors. The Department of Veterans' Affairs (VA) medical centers (VAMC) provide an opportunity to evaluate CRE facility-level risk factors in the largest integrated healthcare system in the United States.

Methods

This ecological study included 136 VAMCs from January 1, 2017, to December 31, 2017, with antibiotic data from January 1, 2016, through December 31, 2016. Facilities were limited to VAMCs with at least 2 of the following care settings: inpatient, outpatient, residential, and/or institutional extended care.

The VA Corporate Data Warehouse (CDW) was used to identify CRE/CP-CRE cases and to collect microbiology, antibiotic, and facility characteristic data. The CDW is a continuously updated relational database of VA clinical and administrative data.[3] CRE cases included *Escherichia coli*, *Klebsiella pneumoniae/oxytoca*, and *Enterobacter* spp resistant to imipenem, meropenem, and/or doripenem. CP-CRE was defined as a positive diagnostic test for carbapenemase production (eg, PCR). Specialty care units were identified if corresponding clinical programs were present at a VAMC. VAMCs were classified by complexity: levels 1a–c were high complexity and levels 2–3 were low complexity. Complexity was based on patient characteristics, clinical programs, and teaching programs. Geographic region was based on US Census region, with Puerto Rico grouped in the Southern region. A facility was affiliated with an academic medical center if it had a training program for health professionals. Antibiotic rates were calculated by total days a patient was prescribed an antibiotic class divided by unique patients. Facility average length of stay was defined as total length of stay divided by cumulative admissions. Intensive care unit (ICU) admission was defined as cumulative ICU admissions for a facility. *International Classification of Disease, Tenth Revision* (ICD-10) procedure codes were used to identify inpatient surgeries and outpatient procedures (Current Procedural Terminology (CPT)/Healthcare Common Procedure Coding System (HCPCS)). Facility CRE rate was calculated as the number of cases divided by the total unique patients.

Bivariate analyses were conducted using the χ^2 or Fisher exact test and the Mann-Whitney U test to assess the association of facility characteristics and the presence or absence of CRE. A P value <.05 was considered significant. Analyses were conducted using STATA version 14.2 software (StataCorp, College Station, TX). ArcGIS software (Redlands, CA) was used to geographically display data.

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Table 1. Frequency of Facility Characteristics and Comparison of Facilities With and Without CRE, 2017

Variable	Facilities (N=136), No. (%)	Facilities with CRE (N=96), No. (%)	Facilities with no CRE (N=40), No. (%)	*P* Value
Facility complexity level				
High	91 (67)	75 (78)	16 (40)	<.0001
Low	45 (33)	21 (22)	24 (60)	
Geographical region				
Northeast	26 (19)	16 (17)	10 (25)	.001
South	48 (35)	42 (44)	6 (15)	
Midwest	32 (24)	24 (25)	8 (20)	
West	30 (22)	14 (15)	16 (40)	
Urban/Rural designation				
Urban	108 (79)	82 (85)	26 (65)	.007
Rural	28 (21)	14 (15)	14 (35)	
Affiliated with an academic center				
Yes	121 (89)	90 (94)	31 (76)	.006
No	15 (11)	6 (6)	9 (23)	
Specialty care units				
Spinal cord injury unit				
Yes	25 (18)	22 (23)	3 (8)	.034
No	111 (82)	74 (77)	37 (92)	
Interventional radiology unit[a]				
Yes	65 (48)	51 (54)	14 (35)	.047
No	70 (52)	44 (46)	26 (65)	
Radiation oncology unit[a]				
Yes	39 (29)	33 (35)	6 (15)	.021
No	96 (71)	62 (65)	34 (85)	
Blind rehabilitation unit				
Yes	13 (10)	10 (10)	3 (8)	.598
No	123 (90)	86 (90)	37 (92)	
Polytrauma unit				
Yes	25 (18)	22 (23)	3 (8)	.034
No	111 (82)	74 (77)	37 (92)	
Performs cardiac surgeries				
Yes	42 (31)	36 (38)	6 (15)	.010
No	94 (69)	60 (62)	34 (85)	
Invasive cardiac catheterization lab				
Yes	67 (49)	55 (57)	12 (30)	.004
No	69 (51)	41 (43)	28 (70)	
Performs neurosurgery				
Yes	45 (33)	37 (39)	8 (20)	.036
No	91 (67)	59 (61)	32 (80)	
		Mean ± SD		
Average length of stay, d	21.8±21.4	18.7 ± 12.0	30.0 ± 34.0	.4505
ICU admissions	136.4 ± 132.1	160.3 ± 139.1	79.2 ± 92.1	.0007
Rate of antibiotic use (days per unique patient)				
Total	3.88 ± 1.23	3.85 ± 1.12	3.97 ± 1.46	.8076
Carbapenem	0.0016 ± 0.0038	0.0016 ± 0.0037	0.0015 ± 0.0042	.0285

(*Continued*)

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Table 1. (*Continued*)

Variable	Facilities (N=136), No. (%)	Facilities with CRE (N=96), No. (%)	Facilities with no CRE (N=40), No. (%)	*P* Value
Third-generation cephalosporin	0.041 ± 0.042	0.043 ± 0.044	0.36 ± 0.038	.5068
Fourth-generation cephalosporin	0.00089 ± 0.0041	0.0011 ± 0.0048	0.00038 ± 0.0021	.0021
Quinolone	0.49 ± 0.24	0.52 ± 0.24	0.41 ± 0.21	.0100
Unique patients with transplant at facility[a]	27.3 ± 27.4	30.3 ± 28.3	20.2 ± 23.8	.0060
Unique inpatient surgeries at facility[b]	817.7 ± 638.9	899.5 ± 666.9	551.2 ± 453.03	.0148
Unique outpatient procedures at facility	87,163.2±45,211.1	96,500.2±47,195.6	64,754.3±30,333.7	.0003

Note. CRE, carbapenem-resistant *Enterobacteriaceae*; CP-CRE, carbapenemase-producing CRE.
[a]1 facility missing.
[b]21 facilities missing.

Results

In total, 801 CRE cases were identified among 7,100,299 unique patients treated in 136 VAMCs (11.3 CRE cases per 100,000 patients), and 97 VAMCs (71%) had at least 1 CRE case. Among CRE cases, 13% were *E. coli*, 26% *Enterobacter* spp, and 61% *Klebsiella pneumoniae* or *K. oxytoca*. Overall, 324 CRE (40%) were CP-CRE. Table 1 describes facility characteristics and comparisons of facilities with and without CRE. A higher proportion of facilities with CRE were high complexity, urban, and were located in the Southern region. Most facilities were affiliated with an academic center, and had spinal cord injury, interventional radiology, radiation oncology units, and invasive cardiac catheterization labs. Most facilities performed neurological and cardiac surgeries. Moreover, increased numbers of ICU admissions, transplants, inpatient surgeries, outpatient procedures, and increased days of carbapenems, as well as higher use of fourth-generation cephalosporins, and quinolones, were associated with facilities with CRE.

We detected significant geographic variation in CRE. The 5 states and territories with the highest numbers of CRE cases were Puerto Rico (n = 224), California (n = 78), New York (n = 76), Texas (n = 59), and Florida (n = 49). The Northeastern, Midwestern, and Western census regions had states with no cases of CRE, whereas all states in the Southern region had at least 1 CRE case (Fig. 1A). The rate of CRE across the United States ranged from 0 to 35.3 cases per 10,000 patients. The highest rates were seen in Puerto Rico, New Jersey (3.48 per 10,000 patients), New York (2.39 per 10,000 patients), Washington, DC (1.89 per 10,000 patients), and Wyoming (1.59 per 10,000 patients) (Fig. 1B).

Discussion

We identified CRE cases in almost three-fourths of VAMCs. Of 801 CRE cases detected, 324 (40%) were CP-CRE. The distribution of organisms identified as CRE in our study was consistent with those of previous studies, with ranges of 2%–15% of *E. coli*, 1%–49% of *Enterobacter* species, and 44%–91% of *Klebsiella pneumonia*/*oxytoca*.[4]

Facility characteristics associated with higher rates of CRE included urban location, high complexity, presence of specific specialty units, greater ICU admissions, and higher numbers of surgeries. In other studies, high-complexity urban facilities are also more likely to treat patients with complex health conditions compared to rural, less complex locations.[5] These patients are often asymptomatic CRE carriers and can mediate transmission to other medically complex patients.[6] Furthermore, higher complexity facilities not only have long-term-care specialty units that increase patient retention, they also have short-term therapeutics in acute care that causes high patient turnover, creating an opportunity for CRE to spread.[5]

We detected significant geographic variation in CRE (Fig. 1A, 1B), with states/territories with the highest CRE cases and rates being in areas with major cities. This finding may relate to greater international travel and population migration in these cities, which could contribute to increased CRE.[7] In contrast to our results, outside the VA, the greatest proportion of CRE cases were observed in the western United States,[8] which could be due to methodological differences in region categorization or different patient characteristics between VA and non-VA facilities. Recognizing variations in regional CRE epidemiology can help hospitals prevent future outbreaks. The interconnective system of healthcare in the VA increases the risk of importing CRE, resulting in greater opportunities for CRE to spread.[5] Failure to control CRE could lead to wider spread due to the ability for CRE to transmit resistance to other gram-negative bacilli.[4]

Finally, facilities with CRE were associated with increased days of carbapenems, fourth-generation cephalosporins, and quinolones, which is similar to patient-level studies.[9] The increasing prevalence of MDR organisms has led to limited therapeutic options and has increased the use of broad-spectrum antibiotics. This antibiotic selective pressure could create an association between broad-spectrum antibiotic use and increased CRE.[10] This finding stresses the importance of monitoring broad-spectrum antimicrobial use to aid the prevention of CRE.

Our study has several limitations. It was an ecological study, with the possibility of ecological fallacy; however, our results were similar to those of patient-level studies.[5,9] Secondly, the sample size was small and precluded the ability to conduct multivariate analyses; however, 136 VAMCs is the largest number of integrated healthcare centers in the United States. Furthermore, CRE/CP-CRE testing is not universal across VAMCs, therefore cases may have been underrepresented and may not reflect the true proportion of CRE/CP-CRE. Furthermore, because we used a laboratory-based definition for CRE, we were not able to differentiate between CRE colonization and infection, or between clinical and surveillance specimens, both of which likely influenced facility-level CRE prevalence rates and may have attributed more cases to facilities that perform active surveillance for colonization.

In conclusion, almost three-fourths of VAMCs had at least 1 CRE case, with significant variation across geographic regions. Infection control strategies targeted to facility characteristics are critical to preventing the spread of CRE. Understanding local

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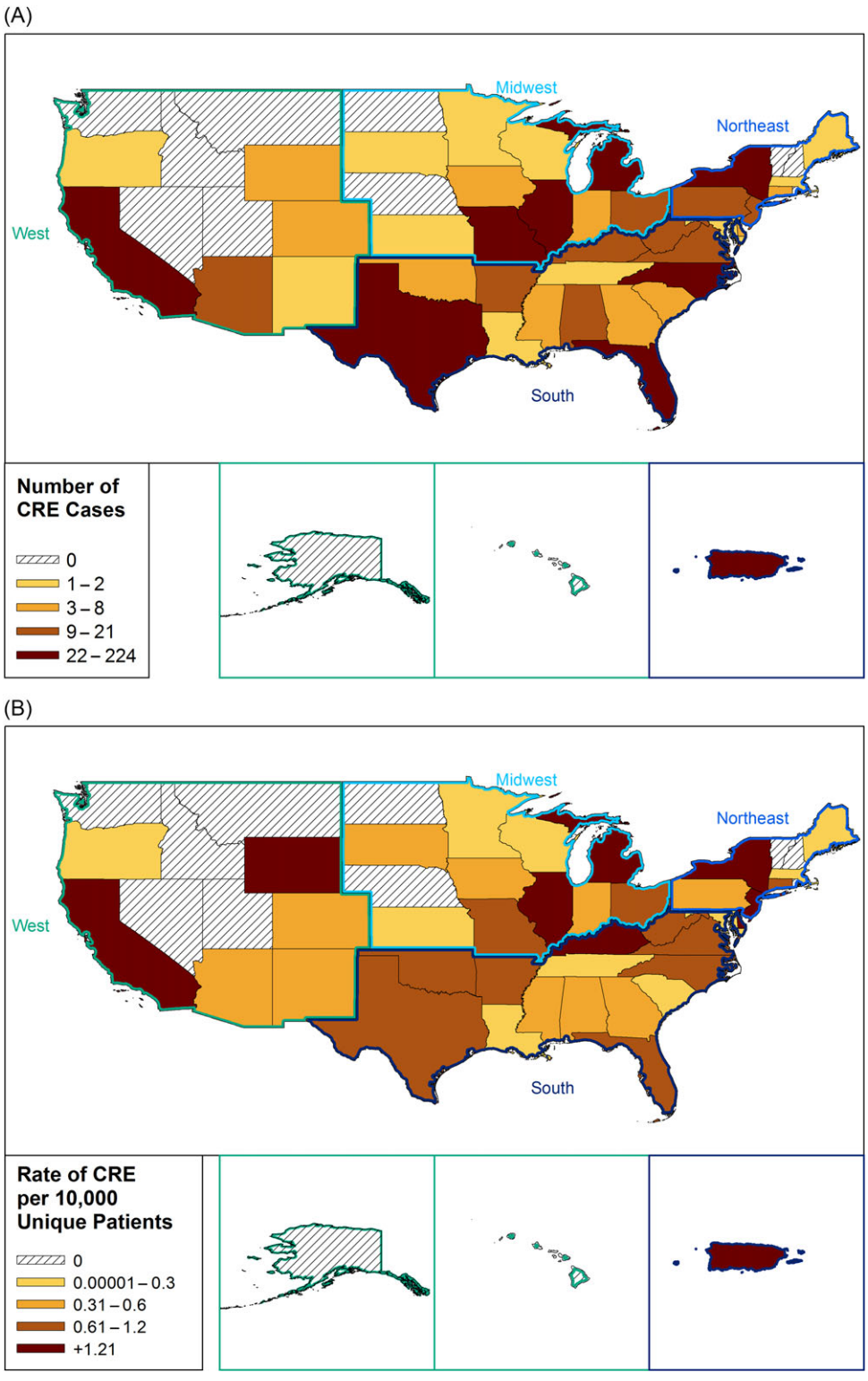

Fig. 1. Geographical distribution of CRE and CP-CRE in the United States, 2017. (A) Number of CRE observations. (B) Rate of CRE per 10,000 patients.

patterns of CRE can help facilities determine where to focus control measures for better prevention of future CRE.

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