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Concise Communication

Uptake in newly approved antibiotics prescribed to patients with carbapenem-resistant Enterobacterales (CRE)

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Abstract

We assessed trends in treatment of patients with CRE from 2012 through 2018. We detected decreased utilization of aminoglycosides and colistin and increased utilization in extended-spectrum cephalosporins and ceftazidime-avibactam. We found significant uptake of ceftazidime-avibactam, a newly approved antibiotic, to treat CRE infections.

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Carbapenem-resistant Enterobacterales (CRE) is classified as an "urgent threat" pathogen.[1] In the United States, the reported CRE incidence is 0.3–2.93 infections per 100,000 person years, with the highest incidence occurring in long-term acute-care facilities.[2] Historically, polymyxins and tigecycline had been considered the drugs of choice for CRE infections. The use of these agents has been complicated by toxicity, limited efficacy, and suboptimal pharmacokinetics.[3] A recent survey of US hospital-based pharmacists showed that new anti-CRE antibiotics, including ceftazidime-avibactam, are positioned as first-line agents for CRE bacteremia >80% of the time.[4] Nevertheless, one study identified lower inpatient utilization of ceftazidime–avibactam. However, this study extrapolated antibiotic purchase data to national CRE estimates and was unable to describe patient-specific treatment.[4] The objective of this study was to describe trends in treatment for patients with cultures positive for CRE.

Materials and methods

This cross-sectional study of CRE treatments was conducted across 134 Veterans' Health Administration (VA) facilities from 2012 through 2018. Patients were identified through the VA Corporate Data Warehouse (CDW). Patients were included in the study if they were aged ≥18 years, had a positive CRE culture, and received a gram-negative antibiotic.

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CRE cultures were defined as *E. coli*, *Klebsiella* spp, or *Enterobacter* spp isolates that were either positive for carbapenemase production by a phenotypic method or were nonsusceptible to imipenem, meropenem, or doripenem. Cultures were categorized either as bloodstream infections (BSIs) or non-BSI cultures, including urine, respiratory, and other cultures. Patients receiving antimicrobials were defined as receiving ≥24 hours of antibiotics 2 days before through 5 days after the CRE culture. The VA has a national drug formulary. After FDA approval in February 2015, ceftazidime–avibactam was added to the formulary, restricted to infectious disease and facility-authorized personnel. Personnel are notified of new additions to the formulary through listservs, education, key program offices (eg, infectious disease), and field representatives.

Continuous data were evaluated with independent *t* tests and 2-way Wilcoxon tests for parametric and nonparametric data, respectively. Categorical data was assessed with a χ^2 test. Poisson regression was applied as a trend test to assess changes in CRE treatment over time stratified by culture source. Two-sided *P* values <.05 were considered significant. SAS version 9.4 software (SAS Institute, Cary, NC) was used for all analyses.

Results

In total, 7,767 patients with positive CRE cultures were identified; 65% (N = 5,082 cultures representing 2,772 unique patients at 111 of 134 facilities) met the definition of receiving antibiotic treatment and were included in the cohort (Table 1). Urine cultures were the major culture source (51.7%) of CRE, followed by respiratory

Table 1. Patient Demographic and Medical Characteristics of carbapenem-resistant Enterobacterales (CRE) Cultures Overall and Stratified by Bloodstream Infection (BSI) and Non-BSI

Characteristic	Overall (N = 5,082)	BSI (N = 697)	Non-BSI (N = 4,385)	*P* Value
Age, mean y (SD)	71.7 (11.8) Range, 19–100 Median, 71	70.5 (12.1) Range, 29–99 Median, 69	71.9 (11.8) Range, 19–100 Median, 71	.0049
Sex, no. (%)				
Male	4,935 (97.1)	661 (13.4)	4,274 (86.6)	.0001
Female	147 (2.9)	36 (24.5)	111 (75.5)	
Comorbidity scores				
Charlson comorbidity Index, mean (SD)	3.7 (3.1) Range, 0–6 Median, 4	3.6 (3.1) Range, 0–14 Median, 3	3.7 (3.1) Range, 0–18 Median, 4	.2158
Gagne index, mean (SD)	12.4 (22.4) Range, 1–195 Median, 0	12.8 (25.4) Range, 1–195 Median, 0	12.3 (21.9) Range, 1–195 Median, 0	.6499
Race and ethnicity, no. (%)				
White, non-Latine	2,041 (40.2)	221 (10.8)	1,820 (89.2)	<.0001
Black, non-Latine	1,208 (23.8)	165 (13.7)	1,043 (86.3)	
Latine	1,590 (31.3)	268 (16.9)	1,322 (83.1)	
Other	77 (1.5)	12 (15.6)	65 (84.4)	
Missing	166 (3.3)	31 (18.7)	135 (81.3)	
Facility geographic region, no. (%)				
Northeast	1,028 (20.2)	111 (10.8)	917 (89.2)	<.0001
Midwest	554 (10.9)	49 (8.8)	505 (91.2)	
South	1,426 (28.1)	226 (15.8)	1,200 (84.2)	
West	612 (12.0)	65 (10.6)	547 (89.4)	
Puerto Rico	1,462 (28.8)	246 (16.8)	1,216 (83.2)	
Facility complexity, no. (%)[a]				
High complexity	4,937 (97.1)	681 (13.8)	4,256 (86.2)	.6245
Moderate complexity	94 (1.8)	10 (10.6)	84 (89.4)	
Low complexity	51 (1.0)	6 (11.8)	45 (88.2)	
Organism isolated in CRE culture, no. (%)				
E. coli	405 (8.0)	37 (9.1)	368 (90.9)	.0042
Klebsiella spp	3,464 (68.2)	505 (14.6)	2,959 (85.4)	.0086
Enterobacter spp	1,213 (23.9)	155 (12.8)	1,058 (87.2)	.0088
Culture location, no. (%)				
Hospital	1,617 (31.8)	227 (14.0)	1,390 (86.0)	.7696
Long-term care	2,725 (53.6)	372 (13.7)	2,353 (86.3)	
Outpatient	162 (3.2)	25 (15.4)	137 (84.6)	
Missing	578 (11.4)	73 (12.6)	505 (87.4)	

[a]VA facilities are classified by complexity: levels 1a–c were high complexity, level 2 was moderate complexity, and level 3 was low complexity. Facility complexity is based on patient characteristics, clinical programs, and teaching programs.

(20.1%), blood (13.7%), and other (14.5%). Most (97.1%) cultures were identified in high complexity facilities, most commonly in the southern United States (28.1%) and Puerto Rico (28.8%). The BSI group was significantly younger than the non-BSI group, but comorbidity scores were similar (Table 1). African Americans and Latines were significantly more likely to have CRE BSI cultures than whites. The frequency of BSI CRE isolates increased significantly (Supplementary Table 1 online).

In total, 4,385 patients with non-BSI CRE cultures received antibiotics: 37.7% received fluoroquinolones, 35.0% received extended-spectrum cephalosporins (cefepime and ceftazidime), 29.8% received penicillins, 29.4% received carbapenems, 21.2% received aminoglycosides, 18.8% received polymyxins, and 4.2% received ceftazidime–avibactam. (Percentages exceed 100% because 36% received multiple antibiotics.) Over the study period, we detected decreased utilization of aminoglycosides (−49.0%;

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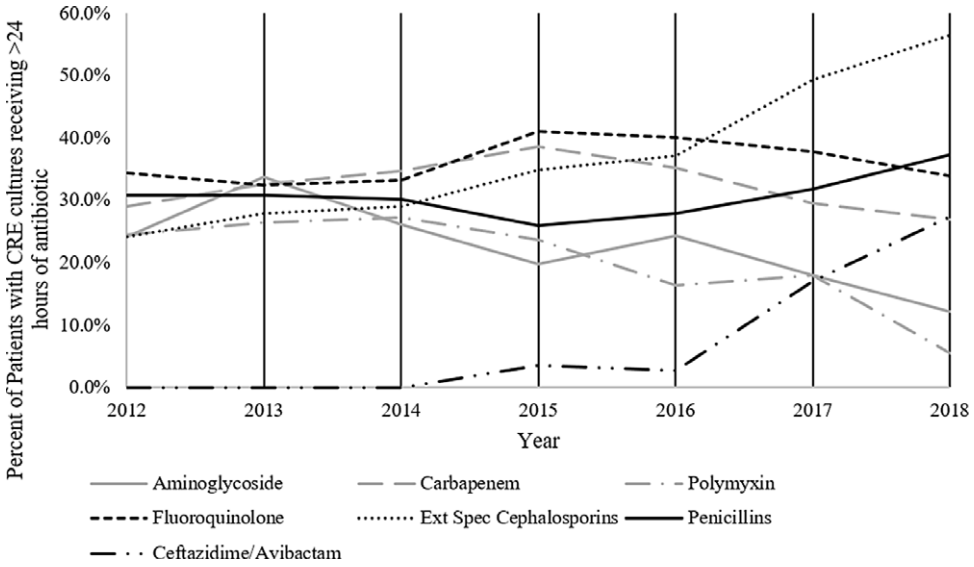

Fig. 1. Trends in antibiotics prescribed to veterans with non-BSI cultures positive for carbapenem-resistant Enterobacterales (CRE). *P* values for trend: aminoglycosides <.0001; carbapenems 0.7985; polymyxins <.0001; fluoroquinolones <.0001; extended spectrum cephalosporins <.0001; penicillins 0.4559; and ceftazidime–avibactam. Ceftazidime–avibactam was approved by the US Food and Drug Administration February 2015 and was available for distribution April 2015. Ceftazidime–avibactam was added to the national VA formulary in December 2015 restricted to infectious disease specialists or facility-authorized provider (when infectious disease specialists are not available at the individual facility). Extended-spectrum cephalosporins included third- and fourth-generation cephalosporins; only ceftazidime and cefepime were prescribed. Cefiderocol was not FDA approved during the study period.

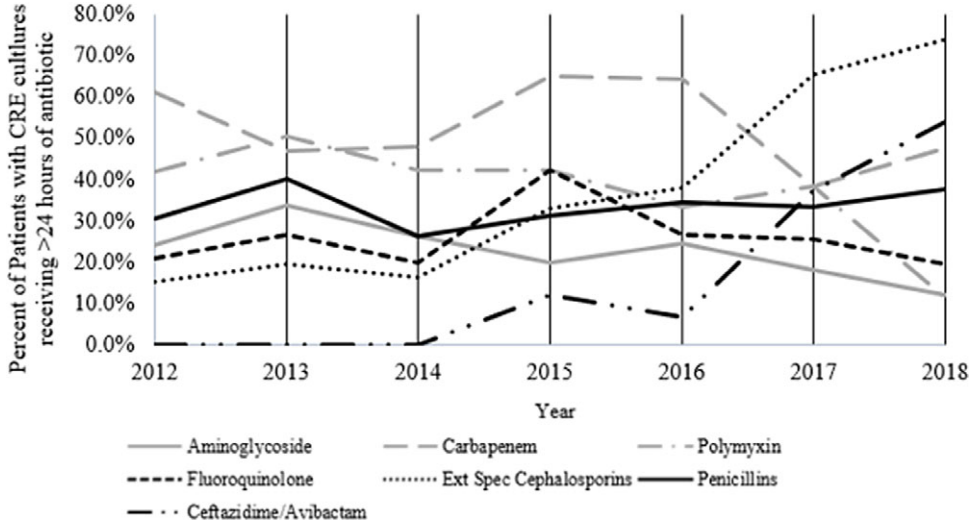

Fig. 2. Trends in antibiotics prescribed to veterans with BSI cultures positive for carbapenem-resistant Enterobacterales (CRE). *P* value for trends: aminoglycosides 0.0026; carbapenems 0.4741; polymyxins .0019; fluoroquinolones .6411; extended spectrum cephalosporins <.0001; penicillins .7110; and ceftazidime–avibactam.[2] Ceftazidime–avibactam was approved by the US Food and Drug Administration February 2015 and was available for distribution April 2015. Ceftazidime–avibactam was added to the national VA formulary in December 2015 restricted to infectious disease specialists or facility-authorized provider (when infectious disease specialists are not available at the individual facility).[3] Extended-spectrum cephalosporins included third- and fourth-generation cephalosporins; only ceftazidime and cefepime were prescribed. Cefiderocol was not FDA approved during the study period.

$P < .001$ for trend) and polymyxins (−79.7%; $P < .001$) and increases in extended-spectrum cephalosporins (111.1%; $P < .001$) and ceftazidime–avibactam (433.0%; $P < .001$) (Fig. 1). In 2018 (the last study year), 22.7% of CRE non-BSI patients received ceftazidime–avibactam and 4.5% received polymyxins (vs 22.2% in 2012).

Among 697 with CRE BSI, 53.4% received carbapenems, 40.3% received aminoglycosides, 39.3% received polymyxins, 32.9% received penicillins, 32.6% received extended-spectrum cephalosporins, 26.1% received fluoroquinolones, and 11.6% received ceftazidime–avibactam. Over the study period, we detected decreases in aminoglycosides (−58.0%; $P < .0026$ for trend) and polymyxins (−72.6%; $P < .002$) and increases in extended-spectrum cephalosporins (385.5%; $P < .001$) and ceftazidime–avibactam (154%; $P < .001$) (Fig. 2). In 2018, 54.1% of CRE BSI patients received ceftazidime–avibactam and 11.9% received polymyxins (vs 41.9% in 2012).

Discussion

This national study was the first to evaluate prescribing trends in patients with confirmed CRE. In the non-BSI and BSI groups, ceftazidime–avibactam use increased dramatically and aminoglycoside and polymyxin use decreased. The significant increase in ceftazidime–avibactam is consistent with the results of a recently published national survey of Infectious Diseases pharmacists, where ceftazidime–avibactam was preferred to polymyxins for CRE.[4] Likewise, national hospital claims demonstrated increases in ceftazidime–avibactam and decreases in polymyxins; however, in contrast to this study, these authors did not confirm that patients had positive CRE cultures.[5] Finally, these results are consistent with IDSA guidance on the treatment of resistant gram-negative infections, which recommend ceftazidime-avibactam and other newer β-lactam antibiotics for CRE infections.[6]

Interestingly, extended-spectrum cephalosporins also increased, likely empiric use prior to confirmed CRE, and may reflect a shift from empiric use of anti-pseudomonal penicillins. Such shifts may have been prompted by increasing recognition during our study period of nephrotoxicity risk with the empiric antibiotic combination of vancomycin and piperacillin–tazobactam.

In this study, persons with CRE-BSI were younger than those with other infection sources. These results echo other findings

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showing that those with BSI were younger than those with hospital- or ventilator-associated pneumonia or complicated urinary tract infections. Additionally, the rate of secondary comorbidities was similar between those with BSI versus other infection types.[7]

Given toxicity concerns, decreases in aminoglycosides and polymyxins were expected. Retrospective studies have demonstrated the association of acute kidney injury (AKI) with polymyxins and aminoglycosides. Observational studies have found improved safety and effectiveness with ceftazidime–avibactam compared with polymyxins.[8] A meta-analysis that evaluated the use of ceftazidime–avibactam in patients with MDR gram-negative infections found the pooled clinical success rate to be 73.3%, similar to polymyxins (66%–79%).[9]

This study had several limitations. Therapies included in this study could have been used for different organisms, which may have overestimated true utilization rates of these antibiotics for CRE. For non-BSI, we were unable to determine definitively whether positive CRE cultures reflected colonization or true infection. Furthermore, because we did not capture antibiotics prescribed >5 days after culture, we may have underestimated ceftazidime–avibactam use, an agent not typically prescribed until a multidrug-resistant organism (MDRO) is identified. This study was conducted in the Veterans Health Administration (VA), which may not be generalizable. Also, other factors may have limited antibiotic utilization, such as drug shortages.

This large national cohort study of veterans with CRE showed an encouraging trend toward increased uptake and utilization of ceftazidime–avibactam for CRE, with decreased utilization of "older" agents such as aminoglycosides and polymyxins. These results are consistent with IDSA and VA guidance, which now recommend ceftazidime–avibactam among the first-line treatments for severe CRE infections. Future studies will need to assess uptake and utilization of other, more recently approved antibiotics targeting multidrug-resistant gram-negative bacteria.

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Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2021.452

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