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Carbapenemase producing *Enterobacterales* at a large teaching hospital in Ohio: comparison to state surveillance and retrospective analysis of patient characteristics

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SUMMARY

Background: The presence of carbapenemase-producing carbapenem-resistant *Enterobacterales* (CP-CRE) around the world is increasing, particularly in healthcare settings. Surveillance testing for plasmid-mediated carbapenemase genes is necessary to tracking CP-CRE infections.

Aim: In the state of Ohio, surveillance of carbapenem-resistant *Enterobacterales* (CRE) began in 2018, and to the authors' knowledge data on these cases has not been published to date. This study analyzed data on CRE from a large teaching hospital in Ohio, and by the Ohio Department of Health Laboratory (ODHL).

Methods: Carbapenemase production was detected using mCIM, and plasmid-mediated carbapenemase genes were detected using rtPCR. Data was collected on 344 standard-of-care isolates from a large teaching hospital in Ohio, including data collected from chart review. Deidentified surveillance data on 4,391 CRE isolates was provided by the ODHL. Statistical analysis was performed using binary logistic regression.

Findings: While KPC was the most common carbapenemase gene (n=1590), NDM (n=98), VIM (n=10), IMP (n=39) and OXA-48 (n=35) were also detected in the isolates studied. *Klebsiella pneumoniae* and *Enterobacter cloacae* were the most common CRE, and carbapenemase genes were most commonly detected in *K. pneumoniae*. Inpatient hospital stays and long-term care were associated with CP-CRE and were more common in women.

Conclusion: Surveillance data shows that CP-CRE are present in Ohio, most commonly in *Klebsiella pneumoniae*. A better understanding of the prevalence of CRE, plasmid-mediated carbapenemase genes present, and the populations affected are important when tracking the spread of disease. Further study and surveillance of carbapenem-resistant organisms can provide a better understanding of their prevalence in the state.

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Introduction

Carbapenem resistant Gram-negative bacteria pose a risk to public health around the world, particularly in healthcare settings, due to overuse of antibiotics and the spread of plasmid-mediated carbapenemase genes [1—3]. Plasmid-mediated genes are particularly concerning due to their ability to spread readily to other bacterial species. Notable plasmid-encoded carbapenemases are KPC, NDM, VIM, IMP and OXA-48 [2]. KPC, a Class A β-lactamase, is the most common carbapenemase found in the United States. It can be differentiated by subtype as KPC-1, 2 or 3, which can vary in antibiotic susceptibility [2,4,5]. Class B β-lactamases includes NDM, VIM and IMP, and the most notable Class D β-lactamases is OXA-48. All four of these are found more commonly outside of the United States [2,5]. Alternate carbapenem resistance mechanisms include outer membrane porin (OMP) alteration or downregulation, penicillin-binding protein (PBP) alteration, and the formation of efflux pumps [1,3].

Factors such as age, previous hospitalization, indwelling medical devices and previous antibiotic treatment have been found to be associated with carbapenem resistant *Enterobacterales* (CRE) infection [3,6—9]. Treatment of CRE infections depends on bacterial mechanisms of resistance, site of infection, and patient co-morbidities [10,11]. Antibiotics such as aminoglycosides, polypeptides, tigecycline, aminoglycosides and fosfomycin have been used successfully, as well as newer drugs including ceftazidime-avibactam (Avycaz®) or meropenem-vaborbactam (Vabomere®). [3,10—13].

At the start of this study CRE surveillance was beginning in the state of Ohio. An aim of this study was to evaluate the plasmid-mediated carbapenemase genes present in the state and the bacterial species that carry them. In addition, we sought to gain an understanding of the at-risk patient population using data from a large academic medical center. This study includes data collected from CRE isolates collected at a large teaching hospital from October 2010 through December 2020, as well as surveillance data provided by the Ohio Department of Health Laboratory (ODHL) from March 2018 through December 2020. Data from these two sources were compared to better understand the types of CRE present in the large academic medical center when compared to the state as a whole. The hospital participating in this study does not currently actively screen for CRE due to low infection rates, however increasing rates of infection detected during surveillance, or possible outbreaks may necessitate implementing screening of high-risk patients and possible environmental reservoirs [14—16].

Methods

Isolate selection

Three-hundred and forty-four *Enterobacterales* isolates from 330 patients were included from non-duplicative standard-of-care specimens, all of which were carbapenem non-susceptible by standard-of-care minimum inhibitory concentration (MIC) testing. Additionally, deidentified data was provided by ODHL regarding 4,391 CRE isolates submitted for testing from the entire state from March 2018 through December 2020.

Study protocols were approved by the Institutional Review Boards prior to the start of this study and were reviewed annually.

Testing scheme

CRE isolates collected prior to March 2018 were frozen as part of standard-of-care testing. CRE were detected by susceptibility testing and carbapenemase production was detected using Modified Hodge Test (MHT) prior to January 2016, and by Rapid CarbaNP after January 2016. As part of this study, isolates were tested for carbapenemase production using modified carbapenem inactivation method (mCIM), and for specific plasmid-mediated carbapenemase genes using rtPCR. The bacterial identification of all isolates was confirmed prior to testing, and carbapenem resistance was confirmed using Ertapenem. Isolates collected starting in March 2018 were sent to ODHL for mCIM and rtPCR testing as part of their surveillance program.

Patient clinical data

Patient characteristics were collected though chart review using the participating medical center's electronic medical record system. This included: patient age, sex, visit type, history of care in long-term care facility, presence of medical devices, travel history (if noted), patient comorbidities and antimicrobials received in the 30 days prior to specimen collection.

Standard-of-care testing

Bacterial identification

Bacterial identification was confirmed using the Bruker or the bioMérieux Vitek® MS Matrix-Assisted Laser Desorption Ionization-Time of Flight (MALDI-TOF) technology.

Susceptibility testing

Standard-of-care susceptibility testing was performed using Beckman Coulter MicroScan prior to February 2018. From February 2018 onward, susceptibility testing was performed using bioMérieux Vitek® 2 system using VITEK 2® GN81. Susceptibility was determined using CLSI guidelines [17]. Ertapenem and ceftazidime/avibactam MIC were determined by E-test.

E-test

Ertapenem, and ceftazidime-avibactam susceptibilities were performed according to bioMérieux E-test package inserts [18].

Colistin agar test

Colistin susceptibility testing was performed by Mayo Clinical Laboratories using the CLSI-approved Colistin agar test for *Enterobacterales* [19]. Non-susceptibility was determined using CLSI guidelines [17].

Surveillance program testing

mCIM

mCIM was performed as per the CLSI guidelines [17].

PCR

A multiplex real time PCR (rtPCR) assay detecting bla_{kpc}, bla_{ndm}, bla_{oxa-48}, bla_{vim} and bla_{imp} genes was performed on mCIM positive or indeterminate isolates. Briefly, bacterial template DNA was prepared by boil prep. Positive and negative controls for each gene were included in each PCR run as well as a non-template (no DNA) control well. The 16s gene was also detected in each well containing a specimen or control organism as an internal control. Quantifast Probe PCR Master Mix (2x) was used for amplification, which was performed using the ABI 7500 Fast Dx Instrument and software. *Klebsiella pneumoniae* ATCC 1706 was used as a negative control. The positive control organisms [20] used for each gene were:

a. bla_{kpc}: *Klebsiella pneumoniae* ATCC 1705
b. bla_{ndm-1}: *Klebsiella pneumoniae* ATCC 2146
c. bla_{OXA-48}: *Klebsiella pneumoniae* AR Bank #0066
d. bla_{VIM}: *Pseudomonas aeruginosa* AR Bank #0100
e. bla_{imp-34}: *Klebsiella pneumoniae* AR Bank #0034
f. bla_{imp-14}: *Pseudomonas aeruginosa* AR Bank #0092

Statistical analysis

Data was analyzed using binary logistic regression, using IBM SPSS statistics software. Collinearity was checked using IBM SPSS statistics software. For categorical variables, one category was required to be used to compare the remaining categories' odds ratios (O.R.). An O.R. greater than 1 indicates that a variable is more likely to be associated with the noted outcome, and an O.R. less than 1 indicates that the variable is less likely to be associated with the outcome. Each O.R. was reported with a p value. A p value of <0.05 was used to determine statistical significance of the results.

Results

Approximately half (56.1%) of the 344 isolates included from the participating medical center were positive for carbapenemase production by mCIM, and one had an indeterminate result. bla_{KPC} and bla_{NDM} were most commonly detected. One isolate was positive for bla_{IMP} and one isolate of *K. pneumoniae* carried both bla_{NDM} and bla_{OXA-48} (Table I). *Serratia marcescens* isolates that were susceptible to third generation cephalosporins but resistant to carbapenems were not tested using PCR due to probable SME gene presence [2]. Other *Serratia* isolates were tested for plasmid-mediated carbapenemase genes. Two isolates of *Enterobacter cloacae* complex tested indeterminate or positive for carbapenemase production by mCIM but no genes were detected by PCR (Table I). Patient age at the time of specimen collection ranged from 19 to 92 years, with an average of 59 years and the majority were male. Most patients were residents of Ohio (n=315); 12 lived in another state and the location of three patients was unknown. Past medical history was unknown for three patients and antibiotic history was unknown for 21 patients. Chronic illnesses or injury requiring long-term medical care were common among patients with available medical records (Table II).

Urine, respiratory, and blood were the most common specimen sources (Table II). Many isolates were collected from a source associated with a medical device, commonly urinary catheters, vascular catheters and respiratory devices. Blood, sterile body fluid, and abscess sources were highly associated with medical devices (Table II). Most isolates were collected during inpatient visits, and residence in a long-term care facility was common (Table II). When categorized by antibiotic class, the most common antibiotics received within 30 days prior to specimen collection were glycopeptides, or a β lactam along with a β lactamase inhibitor (Table II).

Statistical analysis of data collected by patient chart review was performed to study associations between patient characteristics and the presence of carbapenemase producing CRE (CP-CRE). Carbapenemase production (mCIM positivity) was used as the dependent variable, and independent variables in the model were the patient characteristics listed in Table II. Twenty-eight patients were excluded from analysis due to incomplete medical or antibiotic history. Women were found to be more likely to be infected with CP-CRE than men. Patients from long-term care facilities were also more likely to carry a CP-CRE than patients not noted to be in long-term care (Table II). Receipt of a quinolone antibiotic in the 30 days prior to specimen collection were more likely to be associated with CP-CRE than patients who did not receive one (Table II).

Several isolates were found to be resistant to antibiotics commonly used to treat CRE such as colistin, ceftazidime-avibactam and meropenem-vaborbactam. Ceftazidime-

Table I
Polymerase chain reaction (PCR) results of retrospectively collected isolates (October 2010—December 2020)

Organism (n)	mCIM positive or indeterminate	KPC	NDM	IMP	OXA48	VIM	Unknown
***Citrobacter* sp. (13)**	13	13	0	0	0	0	0
***Escherichia coli* (36)**	16	13	3	0	0	0	0
***Enterobacter cloacae* complex (113)**	52[a]	47	3	0	0	0	2
***Hafnia* sp. (9)**	0	0	0	0	0	0	0
***Klebsiella aerogenes* (15)**	1	1	0	0	0	0	0
***Klebsiella oxytoca* (12)**	10	10	0	0	0	0	0
***Klebsiella pneumoniae* (126)**	97	95	1	0	1	0	0
***Morganella morganii* (1)**	1	0	0	1	0	0	0
***Proteus mirabilis* (5)**	0	0	0	0	0	0	0
***Providencia* sp. (5)**	1	0	1	0	0	0	0
***Serratia marcescens* (9)**	2	1	0	0	0	0	1
Total (344)	193	180	8	1	1	0	3

[a] One indeterminate.

Table II
Demographics and statistical analysis of case-patients October 2010–December 2020

Patient characteristic		Number of patients (%)	p	OR (95% CI)
Sex (n = 330)[a]	Male	196 (59.4%)	<0.001	0.316 (0.161–0.620)
	Female	134 (40.6%)	<0.001	3.162 (1.612–6.202)
Age at time of specimen collection (n = 344) [a]	0-19 years	1 (0.3%)	0.047	0.978 (0.956–1.000)
	20-39 years	46 (13.4%)		
	40-59 years	125 (36.3%)		
	60-79 years	151 (43.9%)		
	80-99 years	20 (5.8%)		
	Unknown	1 (0.3%)		
Event type (n = 344)[a]	Inpatient	292 (84.9%)	0.035	2.696 (1.070–6.790)
	Outpatient	47 (13.7%)	0.035	0.371 (0.147–0.934)
	Unknown	5 (1.5%)	-	-
Patients in long term care [a]	Nursing home	65 (19.7%)	0.002	3.876 (1.619–9.277)
Comorbidities	Immunocompromised	57 (17.3%)	0.840	0.896 (0.309–2.597)
	Cancer[a]	97 (29.4%)	0.027	0.446 (0.219–0.911)
	Organ transplant	36 (10.9%)	0.291	0.496 (0.135–1.822)
	Diabetes	116 (35.2%)	0.311	1.393 (0.733–2.647)
	Cardiac/vascular disease	123 (37.3%)	0.792	0.916 (0.476–1.760)
	Renal disease	106 (32.1%)	0.278	1.457 (0.738–2.877)
	Respiratory disease	96 (29.1%)	0.150	1.625 (0.839–3.148)
	Liver/pancreas/ gastrointestinal disease	62 (18.8%)	0.839	0.893 (0.298–2.673)
	Functional limitation/trauma	76 (23.0%)	0.573	1.252 (0.573–2.733)
	Device associated	200 (58.1%)	0.184	0.646 (0.339–1.232)
Specimen source (n = 344)	**Total (n = 344)**	**Device-associated (n = 200)**	**p**	**OR (95% CI)**
Abscess	6 (1.7%)	3 (50%)	0.366	2.705 (0.313–23.379)
Body fluid	19 (5.5%)	14 (73.7%)	0.127	0.366 (0.101–1.329)
Blood	33 (9.6%)	26 (78.8%)	0.711	0.803 (0.251–2.566)
Surgical wound/ bone[a]	22 (6.4%)	3 (13.6%)	0.038	0.244 (0.064–0.928)
Respiratory	80 (23.3%)	65 (81.3%)	-	-
Urine	161 (46.8%)	82 (50.9%)	0.484	1.357 (0.578–3.187)
Wound	23 (6.7%)	7 (30.4%)	0.148	0.346 (0.082–1.458)
Antibiotics rceived 30 days prior to specimen collection				
Antibiotic Class		**Case-patients received drug (n = 344)**	**p**	**OR (95% CI)**
Aminoglycoside		32 (9.3%)	0.480	1.453 (0.516–4.088)
Anamysin[a]		24 (7.0%)	0.009	0.155 (0.039–0.626)
Carbapenem		87 (25.3%)	0.140	0.577 (0.278–1.199)
Cephalosporin	1st generation[a]	21 (6.1%)	0.023	0.234 (0.067–0.819)
	2nd generation	65 (18.9%)	0.610	0.826 (0.396–1.722)
	3rd generation	65 (18.9%)	0.112	0.530 (0.242–1.159)
	4th generation[a]	91 (26.5%)	0.002	0.318 (0.151–0.668)
	5th generation	7 (2.0%)	0.907	0.850 (0.055–13.022)
Glycopeptide		179 (52.0%)	0.144	1.712 (0.832–3.524)
Lincosamide		19 (5.5%)	0.642	0.717 (0.175–2.926)
Lipopeptide		44 (12.8%)	0.144	2.246 (0.759–6.642)
Macrolide		33 (9.6%)	0.819	0.900 (0.364–2.224)
Monobactam		6 (1.7%)	0.240	3.943 (0.399–38.958)
Oxazodilone[a]		48 (14.0%)	0.034	2.682 (1.076–6.684)
Polypeptide		22 (6.4%)	0.749	0.811 (0.225–2.920)

β lactam/β lactam inhibitor	165 (48.0%)	0.314	0.806 (0.529−1.227)
Quinolone[a]	66 (19.2%)	<0.001	4.153 (1.847−9.337)
Tetracycline[a]	13 (3.8%)	0.005	0.055 (0.007−0.417)
Sulfonamide[a]	41 (11.9%)	0.010	4.027 (1.387−11.690)

Note: β-lactam/β-lactam inhibitor includes piperallicin-tazobactam, ampicillin-sulbactam and amoxicillin-clavulanate.
[a] Statistically significant values.

avibactam resistant isolates included three NDM-producers, one KPC-producing *Citrobacter youngae*, and four non-carbapenemase producers. Two of the ceftazidime-avibactam-resistant NDM-producers were also resistant to meropenem-vaborbactam (data not shown) (see Table III).

Statistical analysis was used to assess microbial resistance to select antibiotics in relation to antibiotic use in the 30 days prior to specimen collection, carbapenemase gene presence, and bacterial identification. MIC results (susceptible versus non-susceptible) for each antibiotic served as dependent variables. Independent variables included in the regression model were organism identification, presence of carbapenemase production, total number of antibiotics received, and whether antibiotics of the same class had been received in the 30 days prior to specimen collection. Standard-of-care susceptibility (MIC) results were used for analysis and were chosen because most or all isolates had a documented susceptibility result. Twenty-seven cases that included eighteen KPC-producers (*K. pneumoniae* (10), *E. cloacae* complex (3), *K. oxytoca* (3), *E. coli* (1) and *C. freundii* (1)) and nine non-carbapenemase producers (*E. cloacae* complex (4), *K. aerogenes* (2), *K. pneumoniae* (1), *E. coli* (1), and *P. mirabilis* (1)) were excluded from analysis due to missing MIC results or antibiotic history. Non-susceptibility to amikacin, gentamicin/tobramycin, and ciprofloxacin were all associated with carbapenemase producing organisms. Ciprofloxacin and trimethoprim-sulfamethoxazole non-susceptibility were more likely to occur following the use of fluoroquinolones and sulfonamides, respectively. Antibiotic resistance was generally less associated with bacterial species than with carbapenemase production or prior antibiotic use (Table IV).

In addition to data collected using retrospective isolates, deidentified CRE data collected by the state public health laboratory (ODHL) from March 2018 through December 2020 was available for analysis. This included 4,391 *Enterobacterales* isolates, all of which were determined to be carbapenem non-susceptible upon standard-of-care testing. These isolates were then sent to ODHL for mCIM and PCR testing. Most isolates were *K. pneumoniae* and *Enterobacter species*. The majority (83.2%) of *K. pneumoniae* isolates were mCIM positive and most of these produced KPC. Carbapenemase production was less common in *Enterobacter species* isolates, occurring in 14.7% of isolates. KPC was the most common carbapenemase detected by PCR followed by NDM (Table V). Other less common species were also found to carry carbapenemase genes. KPC was common in both *K. oxytoca* and *Citrobacter sp.* (Table V). Fifty-five of the mCIM-positive *Serratia marcescens* isolates were not tested for carbapenemase genes due to probable SME gene presence. However, a carbapenemase gene was detected in 31 of those tested using rtPCR. (Table V). The number of KPC-producing CRE increased each year from 2018-2020 but the percentage of KPC-producers among total isolates submitted dropped after the first year. The number of OXA-48-producing CRE decreased each year. In contrast, the number of NDM-producers increased each year and VIM-producing CRE increased in 2020 (Table VI).

Statistical analysis was performed using state surveillance data. Positive mCIM results were assessed in their relationship to organism identification, specimen site and region of the state where the specimen was collected. When compared to the participating medical center, CP-CRE were more likely to be detected in the Northeast and West Central regions of Ohio, and less likely in the Southeast. *K. pneumoniae*, *K. oxytoca*, and *Raoultella* sp. were more likely than *E. coli* to produce a carbapenemase, while *Enterobacter, Morganella, Proteus,* and *Providencia* species were less likely than *E. coli* to produce a carbapenemase. When compared to CRO isolated from respiratory sources, those from abscesses, urine, and sterile body fluids were all less likely to produce a carbapenemase (Table V). While urine was the most common specimen type, 1,147 (37.2%) of the 2,818 urine isolates were carbapenemase producers. Of the 485 respiratory culture isolates, 277 (57.1%) were carbapenemase producers.

Discussion

In this study, KPC is the most common carbapenemase present in *Enterobacterales* in Ohio, most commonly in *K. pneumoniae*. However, Class B and D carbapenemases have

Table III
Select antibiotic susceptibility results of retrospectively collected isolates (October 2010−December 2020)

Select susceptibility results from standard-of-care testing				
	Total tested	Susceptible	Intermediate	# Resistant (%)
Amikacin	339	282	41	16 (4.7%)
Avycaz (Ceftazidime/avibactam)	85	77	0	8 (9.4%)
Ciprofloxacin	340	128	13	199 (58.5%)
Colistin	221	0	195	26 (11.8%)
Gentamicin	339	230	26	83 (24.5%)
Nitrofurantoin	160	41	37	82 (51.3%)
Tobramycin	339	176	21	142 (41.9%)
Trimethoprim/sulfamethoxazole	338	173	0	165 (48.8%)

Table IV
Analysis of antibiotic resistance related to organism identification, carbapenemase gene presence and prior antibiotic use

Antibiotic resistance	Amikacin		Gentamicin		Tobramycin		Trimethoprim-sulfamethoxazole		Ciprofloxacin	
	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)
Organism ID										
Citrobacter sp.	0.999	0	0.235	2.537 (0.546−11.785)	0.597	1.518 (0.324−7.115)	0.062	5.111 (0.922−28.335)	0.479	0.567 (0.118−2.732)
Enterobacter cloacae complex	0.003	0.101 (0.022−0.465)	0.176	0.540 (0.222−1.318)	0.014	0.325 (0.132−0.798)	0.458	0.737 (0.330−1.648)	<0.001	0.217 (0.090−0.527)
Hafnia sp.	0.999	0	0.999	0	0.999	0	0.999	0	0.999	0
Other *Klebsiella* species	0.998	0	0.040	0.173 (0.033−0.922)	0.011	0.112 (0.021−0.600)	0.073	0.987 (0.014−1.076)	0.018	0.240 (0.074−0.780)
Klebsiella pneumoniae	0.252	1.838 (0.648−5.214)	0.377	0.676 (0.283−1.613)	0.018	2.911 (1.205−7.035)	0.021	2.607 (1.158−5.869)	0.299	1.651 (0.641−4.253)
Serratia marsescens	0.863	0.800 (0.064−10.077)	0.711	1.365 (0.263−7.087)	0.873	0.871 (0.161−4.714)	0.093	0.148 (0.016−1.373)	0.022	0.118 (0.019−0.739)
Other	0.999	0	0.050	4.676 (1.003−21.798)	0.111	3.530 (0.749−16.638)	0.576	1.502 (0.360−6.266)	0.444	1.980 (0.344−11.405)
Carbapenemase gene presence	<.001	7.645 (2.719−21.496)	<.001	4.523 (2.4154−8.471)	<0.001	5.670 (3.101−10.366)	0.502	1.200 (0.705−2.042)	<0.001	2.800 (1.574−4.981)
Antibiotic use in 30 days prior to specimen collection										
Total antibiotics	0.087	1.177 (0.977−1.417)	0.585	1.037 (0.910−1.182)	0.181	1.097 (0.958−1.255)	0.710	1.023 (0.908−1.151)	0.573	0.964 (0.847−1.096)
Aminoglycoside	0.314	1.760 (0.585−5.294)	0.582	0.777 (0.316−1.909)	0.426	1.492 (0.557−3.995)	N/A	N/A	N/A	N/A
Sulfonamide	N/A	N/A	N/A	N/A	N/A	N/A	0.003	3.687 (1.571−8.654)	N/A	N/A
Fluoroquinolone	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.007	2.878 (1.339−6.186)

Table V
Carbapenem-resistant *Enterobacterales* (CRE) in the state of Ohio March 2018–December 31, 2020, n=4391

Organism (n)	# mCIM pos (%)	IMP	KPC	NDM	OXA48	VIM	UNK	*P* value	O.R. (95% CI)
E. coli (398)	149 (37.4%)	0	94	34	20	1	0	-	-
Citrobacter sp. (167)	70 (41.9%)	0	69	1	0	0	0	0.049	1.475 (1.002–2.170)
Enterobacter sp. (1207)[a]	177 (14.7%)	0	142	24	0	7	6	<0.001	0.303 (0.232–0.396)
Hafnia sp. (20)	0 (0.0%)	0	0	0	0	0	0	0.998	0.000
K. aerogenes (420)	12 (2.9%)	0	12	0	0	0	0	<0.001	0.055 (0.030–0.102)
K. pneumoniae (1450)[b]	1206 (83.2%)	0	1157	39	12	1	0	<0.001	7.227 (5.609–9.311)
K. variicola (4)	4 (100.0%)	0	4	0	0	0	0		
K. oxytoca (71)	58 (81.7%)	1	57	0	0	0	0	<0.001	6.895 (3.594–13.229)
M. morganii (148)	4 (2.7%)	3	1	0	0	0	0	<0.001	0.053 (0.019–0.147)
Proteus sp. (235)	31 (13.2%)	18	12	0	0	0	1	<0.001	0.227 (0.146–0.353)
Providencia sp. (84)	19 (22.6%)	17	2	0	0	0	0	0.037	0.544 (0.307–0.963)
Serratia sp. (170)	55 (32.4%)	0	29	0	1	1	24	0.232	0.783 (0.524–1.169)
Raoultella sp. (14)	12 (85.7%)	0	10	0	2	0	0	0.002	11.028 (2.329–52.227)
Aeromonas sp. (1)	1 (100.0%)	0	0	0	0	0	1	0.370	3.095 (0.262–36.511)
Pantoea sp (2)	1 (50.0%)	0	1	0	0	0	0		
Region (n)	**#mCIM pos (%)**	**IMP**	**KPC**	**NDM**	**OXA**	**VIM**	**UNK**	**P value**	**O.R. (95% CI)**
Medical Center (292)	110 (37.7%)	0	101	6	0	0	3	-	-
Central (469)[b]	150 (32.0%)	9	119	13	7	0	3	0.228	1.270 (0.861–1.873)
East Central (54)	26 (48.1%)	1	25	0	0	0	0	0.058	2.129 (0.976–4.644)
Northeast (1860)[a],[b]	1086 (58.4%)	4	1013	43	20	1	7	<0.001	2.175 (1.568–3.017)
Northwest (354)	132 (37.3%)	8	106	11	2	0	5	0.087	1.439 (0.948–2.182)
Southeast (270)	44 (16.3%)	1	39	3	0	0	1	0.028	0.573 (0.322–2.562)
Southwest (749)	125 (16.7%)	4	90	15	4	9	3	0.091	0.717 (0.508–1.427)
West Central (343)	126 (36.7%)	12	97	7	2	0	8	0.038	1.551 (0.398–0.685)
Specimen Source (n)	**# mCIM pos (%)**	**IMP**	**KPC**	**NDM**	**OXA**	**VIM**	**UNK**	**P value**	**O.R. (95% CI)**
Respiratory (485)	277 (57.1%)	0	254	14	5	0	4	-	-
Abscess (64)	23 (35.9%)	1	20	0	1	0	1	0.029	0.446 (0.216–0.921)
Body Fluid (87)	25 (28.7%)	0	18	1	3	2	1	0.030	0.478 (0.976–4.644)
Blood (264)[a]	150 (56.8%)	0	137	3	4	2	5	0.791	1.057 (0.702–1.592)
Stool/genital (27)	15 (55.6%)	0	12	2	0	0	1	0.856	0.909 (0.322–2.562)
Surgical wound (148)	45 (30.4%)	1	37	4	0	0	3	0.542	0.851 (0.508–1.427)
Urine (2818)[a],[b]	1047 (37.2%)	26	932	55	18	6	9	<0.001	0.522 (0.398–0.685)
Wound/skin/swab (465)	200 (43.0%)	10	165	19	4	0	2	0.354	0.847 (0.597–1.203)
Other/Unknown (33)	17 (51.5%)	1	15	0	0	0	1	0.800	0.881 (0.330–2.352)

Note: *K. pneumoniae* and *K. variicola* were combined for statistical analysis due to relatedness and low number of *K. variicola* isolates. *Aeromonas* and *Pantoea* species were combined into "other" for analysis due to low number of isolates.

[a] Two isolates of *Enterobacter* sp. were positive for both KPC and NDM. Both were from the northeast region. One was isolated from blood and one from urine.

[b] One isolate of *K. pneumoniae* was positive for NDM and OXA. It was from the northeast region and isolated from urine. Two additional isolates were mCIM negative but KPC positive. Both were isolated from urine. One was from the northeast and the other from central regions.

been detected by surveillance PCR testing in the area. In particular, NDM was detected more often after 2018, and VIM presence increased in 2020. While this may, in part, bedue to the increased number of isolates submitted for testing in 2019 and 2020, further study can determine if these trends continue. Based on available patient chart review, not all these cases can be attributed to international travel. Chart review of the patients who carried a class B or D-producing CRE revealed a travel history in only 2 cases: one KPC-and-OXA-48-producing isolate of *K. pneumoniae* collected from an abscess, and an NDM-producing isolate of *Providencia stuartii* collected from a respiratory specimen. The patients in the other cases had no noted travel history. This suggests transfer of class B and D carbapenemases independent of travel.

Table VI
Carbapenemase genes detected in CRE isolates in the state of Ohio by year, 2018–2020, n=4391

	2018	2019	2020
IMP	9 (0.9%)	16 (0.9%)	14 (0.9%)
KPC	506 (48.0%)	508 (29.7%)	576 (35.4%)
NDM	14 (1.3%)	42 (2.5%)	42 (2.6%)
OXA-48	15 (1.4%)	14 (0.8%)	6 (0.4%)
VIM	1 (0.1%)	1 (0.1%)	8 (0.5%)
Total isolates submitted	1055	1710	1626

Data collected through retrospective chart review is consistent with existing literature. Patients at risk for CRE infection are commonly associated with inpatient stays or long-term care, have high rates of comorbidity, exposure to antimicrobials and presence of a medical device [3,16]. Women in

this study were more likely to be infected with CP-CRE than men. While more patients included in this study were men, 49.5% of CRE collected from men and 65.7% of CRE collected from women were carbapenemase producers. One recent study also found community-acquired CP-CRE infection to be more common in women than men, particularly in urinary tract infections [21]. Further study may help determine if this association can be found in larger patient populations.

Many isolates collected prior to March 2018 had been pre-screened for carbapenemase production using Modified Hodge test (MHT) or Rapid CarbaNP as part of standard-of-care testing and were tested for carbapenemase genes retrospectively. While Rapid CarbaNP can more accurately detect class B carbapenemase production that MHT, OXA enzyme production can be missed using both methods [22—24]. An unknown number of non-carbapenemase producing CRE may have been excluded because of this. mCIM testing is more sensitive when detecting OXA enzymes compared to Rapid CarbaNP or MHT, and better at detecting class B metalloenzymes than MHT [5,17,22,23,25].

Some isolates were non-susceptible to new antibiotics developed to treat CRE infection, such as ceftazidime-avibactam. This may be due to limitations of the drug's effectiveness against class B carbapenemase-producers and CRE with alternate resistance mechanisms [10,12]. Carbapenemase producers in this study were also significantly associated with aminoglycoside non-susceptibility. Plasmid-mediated aminoglycoside resistance genes have been previously found in CP-CRE, particularly in NDM and OXA-48 producers. [26,27].

The surveillance data available suggests that, while KPC-producers are the most common CRE present in the state, class B and D carbapenemase genes are present in small numbers independent of travel history. Common characteristics of patients with CRE infection align with previous findings, which can help identify which patients should be targeted for screening if it becomes necessary, including those with co-morbidities, antibiotic use or an indwelling medical device, and patients from long-term care facilities [9,16]. Further study of CRE as well as other carbapenem-resistant organisms will provide an opportunity to monitor their prevalence and spread.

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Conflict of interest

None.

Ethics statement

None.

Credit author statement

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