Risk factors of carbapenemase-producing Enterobacterales acquisition among adult intensive care unit patients at a Kentucky Academic Medical Center

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A R T I C L E   I N F O

S U M M A R Y

Background: Acquisition of carbapenemase-producing carbapenem-resistant Enterobacterales (CP-CRE) are associated with negative health outcomes. Our adult intensive care unit (ICU) population has experienced low levels of CP-CRE acquisition; however, specific risk factors for this population at our medical facility have not been studied.
Aims: To identify risk factors of CP-CRE acquisition and describe CP-CRE epidemiology among adult ICU patients at our medical facility.
Methods: A retrospective cohort study was performed at a Kentucky Academic Medical Center. Surveillance specimens were collected at admission and weekly thereafter to identify CP-CRE colonization. Clinical data were extracted from patient medical records. Cases were defined as those who tested positive for CP-CRE on ICU admission day 3 or greater. Risk of CP-CRE acquisition was calculated using Modified Poisson regression.
Findings: Independent risk factors of CP-CRE acquisition included administration of enteral tube feeds (risk ratio [RR], 4.46; 95% confidence interval [CI], 1.74—11.43); diagnosis of *Clostridioides difficile* enterocolitis (RR, 3.51; 95% CI, 1.27—9.68), pressure ulcer (RR, 3.48; 95% CI, 1.91—6.36), and morbid obesity (RR, 2.10; 95% CI, 1.12—3.95); having a drainage tube (RR, 2.63; 95% CI, 1.38—4.98); admission to a medical ICU (RR, 2.39; 95% CI, 1.32—4.35); 90-day use of a carbapenem (RR, 2.27; 95% CI, 1.21—4.26); and dialysis procedure (RR, 2.22; 95% CI, 1.15—4.27).
Conclusion: Most CP-CRE risk factors were associated with alteration of colon microbiota and/or invasive procedures/devices. These results will assist in creating a more targeted

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CP-CRE active surveillance system and highlight areas for infection prevention intervention.

Introduction

Over the past several decades, there has been considerable attention on the steady rise of microbial antibiotic resistance in the United States (US) and around the world. Carbapenem resistance has emerged as an urgent public health concern. Carbapenem-resistant organisms have the ability to break down carbapenems, a class of broad-spectrum β-lactam antibiotics, that are often used as a last resort for Gram-negative bacterial infections. [1] Members of the order Enterobacterales (e.g., *Escherichia*, *Klebsiella*, *Enterobacter*, etc.) are among the most commonly reported carbapenem resistant organisms for causing healthcare-associated infections [2]. Carbapenem-resistant Enterobacterales (CRE), are often resistant to many antibiotics in addition to carbapenems [3]. This may lead to poorer health outcomes including higher mortality due to limited treatment options [4].

Transmission of carbapenem resistance among Enterobacterales has been primarily attributed to carbapenemase-producing CRE (CP-CRE), which have the ability to hydrolyze carbapenems and most β-lactamase inhibitors and in some cases convey pan resistance [5,6]. Due to the high potential of transmission and negative health outcomes, CRE have been classified as an urgent public health threat, the highest hazard classification for antibiotic resistance organisms reported by the Centers for Disease Control and Prevention (CDC) [1].

Our facility, a Kentucky Academic Medical Center (KAMC), implements infection prevention practices in accordance with CDC guidance to reduce CP-CRE acquisition. This includes a CRE active surveillance program. Despite following best practices, we experienced persistent, low levels of healthcare-associated CP-CRE acquisition in the adult intensive care unit (ICU) population. This raised concerns of potential unidentified reservoirs and/or risk factors for CP-CRE acquisition.

There have been numerous studies in the US and internationally that have identified associations between CP-CRE acquisition and specific risk factors (e.g., antibiotic usage, invasive devices and procedures, comorbidities, etc.) [7] Risk factors for CP-CRE may differ between healthcare facilities and their respective patient populations. Currently, there are no published studies regarding CP-CRE risk factors in a Kentucky patient population. We sought to identify specific risk factors of CP-CRE acquisition and to describe CP-CRE epidemiology in an adult ICU population at KAMC. This study differs from most published reports of CP-CRE risk factors in that it takes place within a state classified as one of the most obese and least healthy populations in the US [8]. Knowledge gained from this study will assist KAMC in better targeting the CRE active surveillance program and will be useful in identifying areas that need further infection prevention interventions to prevent CP-CRE acquisition.

Methods

Study setting

Our study is a retrospective cohort study. The cohort includes all adult ICU patients (≥18 years) admitted to the KAMC between October 1, 2013–October 31, 2016. The KAMC is a 945-bed acute tertiary care teaching facility comprised of 2 hospitals on separate campuses. The main hospital includes 7 adult ICU populations (medical [7 physical locations: A, B, C, D, E, F, and G], cardiovascular, neurology, neurosurgical, trauma, surgical, and cardiothoracic) with a total of 136 ICU beds. The second hospital has a 15-bed adult medical/surgical ICU. The KAMC institutional review board (IRB) approved of the study before its initiation (IRB 4834).

Data collection

Exposure data used for this project were provided by the institution's Center for Clinical and Translational Science Enterprise Data Trust. Electronic medical records were retrieved retrospectively by a Data Trust Analyst. Exposure variables included patient demographics, ICU type, ICU length of stay (LOS), medication use, comorbidity scores, medical diagnoses, and invasive devices/procedures. More specifically, drainage tubes include Jackson-Pratt and chest tubes; gastrointestinal-feeding tubes refer to gastrostomy, nasogastric, and oral gastric tubes.

The outcome of CP-CRE acquisition was identified retrospectively from a database maintained by the medical center's Infection Prevention and Control Department. This database included all patients who tested positive for CP-CRE. Acquisition of CP-CRE included both colonization from perirectal and axilla/groin swabs and infections obtained from clinical specimens (e.g., blood, urine, etc.). Acquisition of CP-CRE was defined as the detection of CP-CRE from a patient specimen on admission day 3 or later. All specimens positive upon admission were considered community acquired and were excluded from the study. The CP-CRE case definition was any member of Enterobacterales resistant to a carbapenem and identified as producing carbapenemases via phenotypic modified Hodge test (MHT), metallo-β-lactamase screen, and/or identified with a carbapenemase gene.

Patients in the ICU were screened for CP-CRE upon admission and every Monday following admission. Weekly audits were conducted by infection prevention staff to ensure that admission and follow-up screens were collected. Patients with a positive CP-CRE culture were right censored on the specimen collection date. Patients who did not have a positive CP-CRE culture result were right censored on their last CP-CRE screening date. All ICU patients who did not have at least one follow-up CP-CRE screen (i.e., only screened at admission and

discharged before the Monday follow-up screen) were removed from the study since CP-CRE acquisition for ICU stay could not be determined.

Microbiology

All specimen collection and microbiology analyses were performed by the institution's medical staff and microbiology lab, respectively. Perirectal and axilla/groin surveillance specimens were collected aseptically using an ESwab™ (Copan Diagnostics Inc.) containing Amies transport medium. Clinical specimens were collected using standard microbiological techniques. Surveillance and clinical specimens were plated directly onto agar with vancomycin, amphotericin B, ceftazidime, and clindamycin (VACC Agar). Becton Dickinson Phoenix™, an automated identification and susceptibility testing system, was used to identify isolates on VACC agar and to determine which isolates exhibited carbapenem resistance. The Clinical Laboratory Standards Institute minimum inhibitory concentration (MIC) micrograms per milliliter (μg/mL) breakpoints for carbapenem resistance (i.e., ≥ 4 μg/mL for meropenem, imipenem, and doripenem and ≥ 2 μg/mL for ertapenem) were used to define carbapenem resistance [9]. Isolates exhibiting carbapenem resistance were further screened for carbapenemase production via a MHT and a metallo-β-lactamase ETEST® (bioMérieux Inc.). Beginning June 2014, isolates that tested positive with the MHT or metallo-β-lactamase ETEST® were analyzed for 5 carbapenemase enzymes (i.e., *Klebsiella pneumoniae* carbapenemase [KPC], oxacillinase-48 [OXA], Imipenemase [IMP], New Delhi metallo-β-lactamase [NDM], and Verona integron-encoded metallo-β-lactamase [VIM]) with the Nanosphere Verigene® system. Species identification was accomplished via a Matrix-Assisted Laser Desorption-Ionization-Time of Flight Mass Spectrometry (MALDI-TOF MS).

Data analysis

Analyses account for potential statistical correlation among repeated measures on the same patient, as well as the rarity of our outcome, CP-CRE acquisition. Specifically, we fit marginal, modified Poisson regression models using generalized estimating equation (GEE) with a working AR-1 correlation structure and the use of robust standard error estimates [10,11]. Furthermore, to ensure results target the population, patient-weighting was used in the GEE approach to account for the number of patient admissions (i.e., 1/n where N=number of admissions) [12].

All variables with a P value of ≤ 0.05 in the univariate analysis were considered for inclusion in multivariate analysis. Backwards elimination, using a significance level of ≤ 0.05, was used to select variables into the final multivariate model. An exception to this was the retention of variables without a significant association with the outcome of CP-CRE acquisition, but that were possible confounders. Significance was set at ≤ 0.05 for all analyses. SAS® version 9.4 software (SAS Institute, Cary, NC) was used for all modeling and statistical analyses.

Results

The cohort initially included 15,755 adult ICU patients with approximately 18,895 separate ICU admissions and a total of 81,519 patient days. Patients that were right censored due to being discharged before at least one follow-up CP-CRE swab could be obtained (N=8,536), missing exposure data (N=172), and positive for CP-CRE on admission (N=21) were excluded from the study. Our final study cohort included a total of 7,026 individual adult ICU patients with 7,888 separate admissions (Figure 1).

CP-CRE acquisition

There were 48 CP-CRE acquired cases identified in the study. The majority of CP-CRE were collected on medical ICU A (N=21; Figure 2). Clusters associated spatially and temporally with the same CP-CRE organism and/or carbapenemase occurred on Medical ICU A in February 2015 (KPC *Enterobacter cloacae* [N=2]; KPC *Citrobacter freundii* [N=1]) and in November 2015 (KPC *Enterobacter* spp. [N=2]). Medical ICU A closed in June 2016 with the opening of newly constructed medical ICUs D, E, F, and G; no CP-CREs were identified on these ICUs.

The incidence of CP-CRE acquisition was 5.89 (95% confidence interval [CI], 4.39−7.74) per 10,000 ICU patient days.
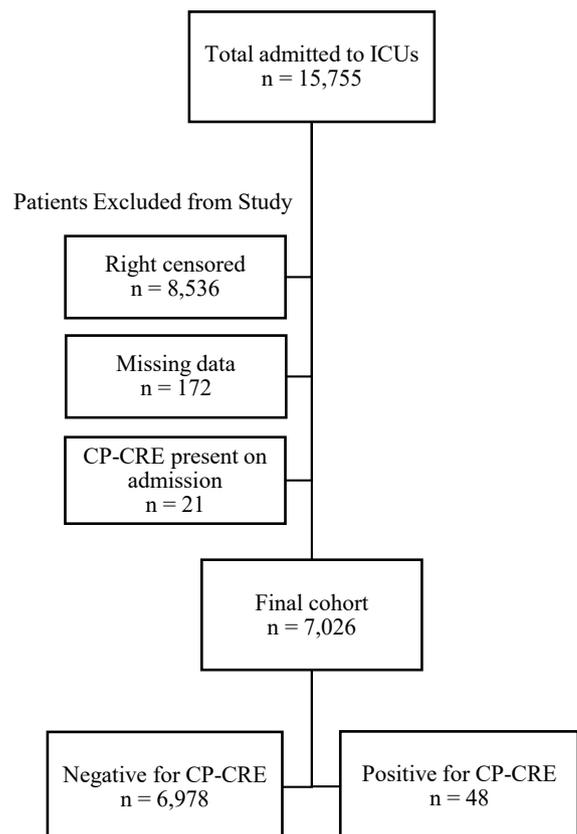

Figure 1. Cohort study flow of adult ICU patients at the Kentucky Academic Medical Center (October 1, 2013−October 31, 2016).
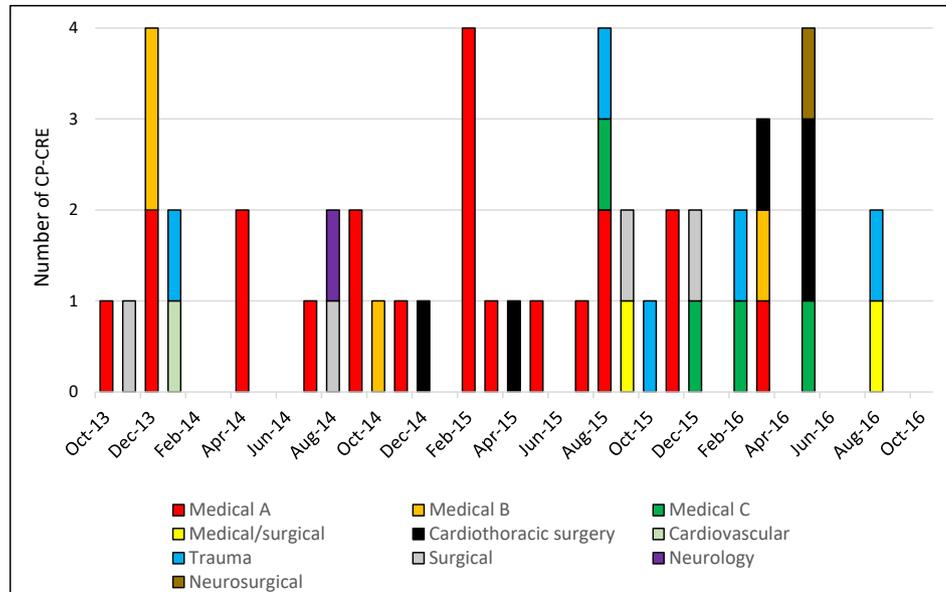
Figure 2. Healthcare-acquired Carbapenemase-Producing Enterobacterales by collection month and intensive care unit collection location at the Kentucky Academic Medical (October 1, 2013—October 31, 2016).

Over 91% of all CP-CRE cases were detected via active surveillance (3 axilla/groin specimens and 41 perirectal specimens). There were only 4 CP-CRE detected from clinical specimens (sputum, bronchoalveolar lavage, wound, and pancreatic fluid). The CP-CRE genera included *Enterobacter* spp. ($N=28$, 58.3%), *Klebsiella* spp. ($N=10$, 20.8%), *Citrobacter* spp. ($N=9$, 18.8%), and *Leclercia* spp. ($N=1$, 2.1%) (Figure 3).

Enterobacter cloacae was the dominant CP-CRE species identified ($N=17$, 35.4%), followed by *C. freundii* ($N=7$, 14.6%), and *K. pneumoniae* ($N=7$, 14.6%).

Carbapenemase genes were detected in 34 of the 48 CP-CRE isolates (70.8%); KPC ($N=24$) and VIM ($N=10$) were the only carbapenemases detected during the study period (Figure 3). Fourteen isolates that tested positive with the MHT were not
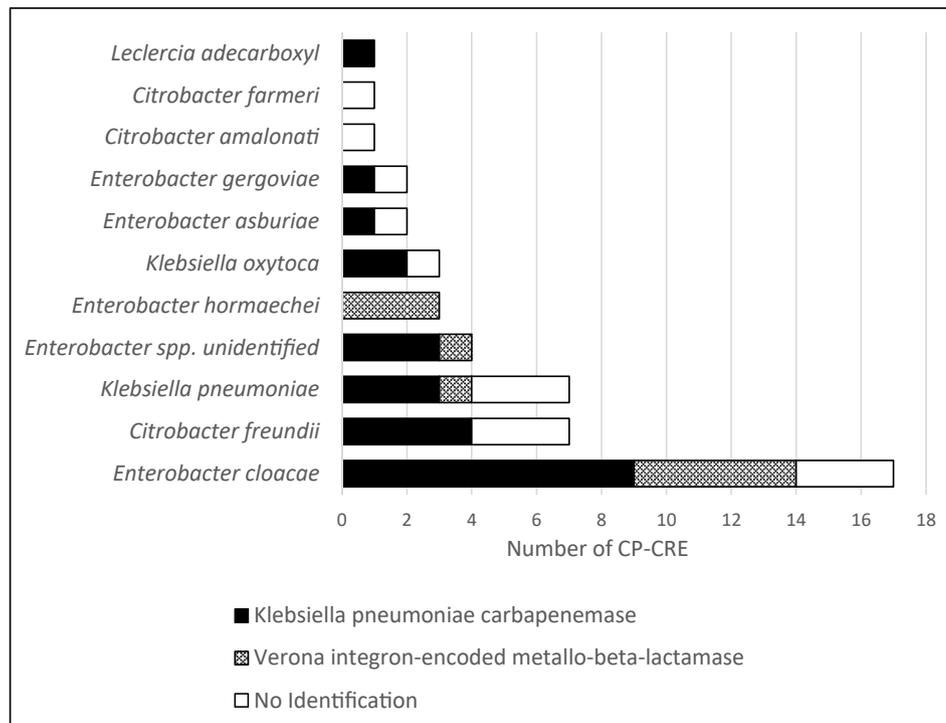

Figure 3. Number of healthcare-acquired Carbapenemase-Producing Enterobacterales by species and carbapenemases among the Kentucky Academic Medical Center's adult intensive care unit patients (October 1, 2013—October 31, 2016).

Table I

Characteristics of adult intensive care unit patients at the Kentucky Academic Medical Center (October 1, 2013–October 31, 2016) by carbapenemase-producing Enterobacterales acquisition

Variable	No CP-CRE acquisition N=6,978	CP-CRE acquisition N=48	P value[a]
Age, mean (SD)	57.8 (16.0)	56.0 (14.1)	0.42
Male Sex (%)	3,954 (56.0)	29 (60.42)	0.60
Race (%)			0.34
White	6,441 (92.3)	47 (97.9)	
Black	491 (7.0)	1 (2.1)	
Other	46 (0.7)	0 (0.00)	
BMI, median (IQR)	28.8 (24.3–34.8)	29.3 (25.4–40.5)	0.24
Morbid Obese (BMI ≥40)	964 (13.8)	14 (29.2)	0.002
Charlson Comorbidity Index (%)			<0.0001
0-3	2,900 (41.6)	8 (16.7)	
4-6	2,950 (42.3)	22 (45.8)	
>6	1,128 (16.2)	18 (37.5)	
ICU Type, ever Admitted (%)			
Medical/Surgical	694 (10.0)	3 (6.3)	0.62
Cardiovascular	335 (4.8)	5 (10.4)	0.07
Medical	2,510 (36.0)	30 (62.5)	<0.0001
Neurology	726 (10.4)	1 (2.1)	0.06
Neurosurgical	661 (9.5)	1 (2.1)	0.08
Trauma	644 (9.2)	7 (14.6)	0.21
Surgical	627 (9.0)	4 (8.3)	1.0
Cardiothoracic surgery	1,126 (16.1)	6 (12.5)	0.49
ICU Type LOS, median (IQR)			
Medical/Surgical	3 (1–6)	7 (4–11)	0.09
Cardiovascular	5 (2–11)	10 (6–10)	0.36
Medical	5 (2–10)	12.5 (7–19)	<0.0001
Neurology	4 (2–9)	3 (3–3)	0.62
Neurosurgical	5 (2–9)	1 (1–1)	0.15
Trauma	4 (2–10)	12 (9–18)	0.01
Surgical	4 (2–10)	12 (3–30)	0.28
Cardiothoracic surgery	5 (3–11)	7.5 (6–9)	0.22
Total ICU LOS, median (IQR)	5 (2–10)	13 (7–20)	<0.0001
Medication Usage (%)			
Aminoglycosides	678 (9.7)	10 (20.8)	0.02
Carbapenems	548 (7.9)	15 (31.3)	<0.0001
Cefazolin	697 (10.0)	5 (10.4)	0.81
Cefepime	1,763 (25.3)	21 (43.8)	0.003
Ceftriaxone	746 (10.7)	9 (18.8)	0.07
Levofloxacin	897 (12.9)	9 (18.8)	0.22
Macrolides	592 (8.5)	8 (16.7)	0.06
Metronidazole	1,490 (21.4)	24 (50.0)	<0.0001
Piperacillin/Tazobactam	1,668 (23.9)	24 (50.0)	<0.0001
Sulfamethoxazole/Trimethoprim	252 (3.6)	4 (8.3)	0.10
Vancomycin	2,845 (40.8)	39 (81.3)	<0.0001
Immunosuppressants	193 (2.8)	4 (8.3)	0.045
Proton Pump Inhibitors	3,143 (45.0)	29 (60.4)	0.03
Medication Dose, median (IQR)			
Aminoglycosides	3 (1–6)	4 (2–12)	0.41
Carbapenems	12.5 (5–36)	8 (2–18)	0.14
Cefazolin	4 (3–12)	31 (4–63)	0.15
Cefepime	9 (4–21)	12 (6–28)	0.19
Ceftriaxone	3 (1–6)	2 (1–4)	0.49
Levofloxacin	3 (1–7)	3 (1–4)	0.71
Macrolides	3 (1–6)	4 (1–7)	0.41
Metronidazole	10 (4–24)	13 (7–25)	0.25
Piperacillin/Tazobactam	14 (6–34)	21 (10–96)	0.08
Sulfamethoxazole/Trimethoprim	6 (3–18)	6 (3.5–12)	0.82

Table I (*continued*)

Variable	No CP-CRE acquisition $N=6{,}978$	CP-CRE acquisition $N=48$	P value[a]
Vancomycin	5 (2−14)	8 (4−22)	0.04
Immunosuppressants	25 (8−93)	19 (5−319)	0.81
Proton Pump Inhibitors	8 (3−20)	16 (9−40)	0.0004
Any Antibiotic Usage (%)	3,926 (56.3)	41 (85.4)	<0.0001
Antibiotic Types (%)			<0.0001
1−3 antibiotics	1,846 (26.4)	7 (14.6)	
≥4 antibiotics	2,098 (29.9)	33 (70.8)	
Diagnoses (%)			
Gram-negative Infection	477 (6.8)	10 (20.8)	0.0001
C. difficile Enterocolitis	118 (1.7)	5 (10.4)	<0.0001
Protein Malnutrition (any level)	1,564 (22.4)	14 (29.2)	0.26
Pressure Ulcer (any stage)	541 (7.8)	17 (35.4)	<0.0001
Sepsis	2,487 (35.6)	36 (75.0)	<0.0001
Urinary Tract Infection	1,203 (17.2)	13 (27.1)	0.07
Diabetes (ever)	1,573 (22.5)	20 (41.7)	0.002
Pneumonia	1,913 (27.4)	21 (43.8)	0.01
Device (%)			
Drainage Tubes	1,876 (26.9)	20 (41.7)	0.02
Enteral Tube Feeds	3,313 (47.5)	43 (89.6)	<0.0001
Dialysis	886 (12.7)	21 (43.8)	<0.0001
Indwelling Urinary Catheter	6,080 (87.1)	48 (100)	0.008
Rectal Tube	260 (3.7)	7 (14.6)	0.002
Gastrointestinal-Feeding Tube	1,387 (19.9)	18 (37.5)	0.002
Device Days, median (IQR)			
Drainage Tubes	4 (3−8)	8 (4−18.5)	0.005
Enteral Tube Feeds	6 (3−14)	10 (5−18)	0.049
Dialysis	6 (3−12)	9 (6−12)	0.03
Indwelling Urinary Catheter	5 (3−10)	12.5 (6.5−20.5)	<0.0001
Rectal Tube	4 (2−8)	4 (2−10)	0.90
Gastrointestinal-Feeding Tube	3 (1−6)	5 (3−7)	0.08

Note. SD, standard deviation; IQR, interquartile range; BMI, body mass index; ICU, intensive care unit; LOS, length of stay; *C. difficile*, *Clostridioides difficile*.

[a] *P* values were obtained using chi-square or Fisher's exact for binary data, *t*-test for normally distributed data, and Wilcoxon Rank Sum Test for nonparametric data.

analyzed for carbapenemases with the Nanosphere Verigene® system due to system unavailability. The incidence density of KPC and VIM carbapenemases acquired during the study period were 2.94 (95% CI, 1.93−4.31) and 1.23 (95% CI, 0.62−2.19) per 10,000 ICU patient days, respectively. Most KPC ($N=9$) and VIM ($N=5$) carbapenemases were identified in *E. cloacae* isolates.

Patient characteristics

The characteristics of the adult ICU patients are presented in Table I. Patients were mostly white (92.3%) and male (56.7%) with an average age of 58. There were no clear differences in age, sex, or race of patients with CP-CRE compared to patients without CP-CRE. Morbid obesity and comorbid conditions were more common among patients with CP-CRE. Medication utilization, diagnoses, and invasive devices/procedures in prior 90 days were also generally more common among patients with CP-CRE compared to those with no CP-CRE acquisition.

Regression analysis

Results from univariate and multivariate regression models for predictors of CP-CRE acquisition are displayed in Table II. There were multiple variables associated with CP-CRE acquisition in univariate analysis. Multivariate regression identified 8 independent risk factors for CP-CRE acquisition including morbid obesity (risk ratio [RR], 2.10; 95% CI, 1.12−3.95); admission to a medical ICU (RR, 2.4; 95% CI, 1.32−4.35); carbapenem usage in prior 90 days (RR, 2.27; 95% CI, 1.21−4.26); diagnosis of *Clostridioides difficile* enterocolitis (RR, 3.51; 95% CI, 1.27−9.68) and pressure ulcer (RR, 3.48; 95% CI, 1.91−6.36) in previous 90 days; and having enteral tube feeds (RR, 4.46; 95% CI, 1.74−11.43), drainage tubes (RR, 2.63; 95% CI, 1.38−4.98), and dialysis (RR, 2.22; 95% CI, 1.15−4.27) in prior 90 days.

Discussion

The incidence of CP-CRE in US healthcare facilities varies and has ranged from 0.30 to 6.83 cases per 10,000 patient days [13,14]. The incidence of CP-CRE acquisition in our study was higher than most (5.89 per 10,000 ICU patient days) and likely reflects differences in study design, CP-CRE definitions, and study populations.

Four VIM CP-CRE, including 3 *Enterobacter hormaechei* isolates, in the Trauma ICU were further analyzed during a CDC investigation [15]. Results concluded that horizontal

Table II
GEE univariate and multivariate modified poisson regression for predictors of carbapenemase-producing Enterobacterales acquisition among adult intensive care unit patients at the Kentucky Academic Medical Center (October 1, 2013—October 31, 2016)

Variable	Univariate RR (95% CI)	*P* value	Multivariate RR (95% CI)	*P* value
Age (per 1 year)	1.00 (0.98—1.01)	0.33		
Male: Sex	1.23 (0.68—2.21)	0.50		
Morbid Obese (≥40 BMI)	2.75 (1.47—5.16)	0.002	2.10 (1.12—3.95)	0.02
Charlson Comorbidity Index				
4-6	3.24 (1.40—7.46)	0.006		
>6	6.18 (2.61—14.66)	<0.0001		
ICU Type, ever admitted				
Medical/Surgical	0.55 (0.16—1.83)	0.33		
Cardiovascular	2.42 (0.96—6.07)	0.06		
Medical	3.18 (1.75—5.78)	0.0001	2.39 (1.32—4.35)	0.004
Trauma	1.83 (0.82—4.08)	0.14		
Surgical	0.74 (0.25—2.16)	0.58		
Cardiothoracic surgery	0.76 (0.32—1.81)	0.53		
ICU type LOS (per 10 days)				
Medical/Surgical	0.93 (0.51—1.70)	0.81		
Cardiovascular	1.11 (0.98—1.25)	0.11		
Medical	1.28 (1.18—1.38)	<0.0001		
Trauma	1.36 (1.14—1.63)	0.001		
Surgical	1.07 (0.85—1.36)	0.56		
Cardiothoracic surgery	0.97 (0.73—1.31)	0.85		
Total ICU LOS (per 10 days)	1.10 (1.07—1.14)	<0.0001	0.95 (0.81—1.11)	0.51
Medication Usage				
Aminoglycosides	2.66 (1.32—5.37)	0.006		
Carbapenems	5.70 (3.07—10.55)	<0.0001	2.27 (1.21—4.26)	0.01
Cefazolin	1.04 (0.40—2.78)	0.94		
Cefepime	2.29 (1.28—4.08)	0.005		
Ceftriaxone	1.92 (0.92—4.03)	0.08		
Levofloxacin	1.42 (0.67—3.00)	0.36		
Macrolides	2.08 (0.96—4.53)	0.06		
Metronidazole	3.55 (2.00—6.32)	<0.0001		
Piperacillin/Tazobactam	3.05 (1.71—5.42)	0.0002		
Sulfamethoxazole/Trimethoprim	2.19 (0.79—6.04)	0.13		
Vancomycin	6.10 (2.93—12.73)	<0.0001		
Immunosuppressants	2.56 (0.88—7.45)	0.08		
Proton Pump Inhibitors	1.96 (1.09—3.54)	0.03		
Medication Dose (per 10 doses)				
Aminoglycosides	1.03 (0.97—1.10)	0.34		
Carbapenems	1.01 (1.00—1.02)	0.26		
Cefazolin	1.04 (1.00—1.09)	0.04		
Cefepime	1.02 (1.01—1.03)	0.0007		
Ceftriaxone	1.00 (0.93—1.06)	0.87		
Levofloxacin	1.07 (0.96—1.19)	0.24		
Macrolides	1.01 (0.99—1.04)	0.36		
Metronidazole	1.02 (1.01—1.03)	0.003		
Piperacillin/Tazobactam	1.01 (1.01—1.02)	0.0004		
Sulfamethoxazole/Trimethoprim	0.94 (0.80—1.10)	0.43		
Vancomycin	1.02 (1.01—1.04)	0.0008		
Immunosuppressants	1.01 (1.00—1.01)	0.19		
Proton Pump Inhibitors	1.00 (1.00—1.00)	0.11		
Any Antibiotic Usage	4.48 (1.98—10.12)	0.0003		
Antibiotic Types				
1—3 antibiotics	1.60 (0.55—4.66)	0.39		
≥4 antibiotics	7.11 (3.10—16.2)	<0.0001		
Diagnoses				
Gram-negative Infection	3.79 (1.88—7.65)	0.0002		
C. difficile Enterocolitis	5.90 (2.28—15.27)	0.0002	3.51 (1.27—9.68)	0.02

Table II (*continued*)

Variable	Univariate RR (95% CI)	P value	Multivariate RR (95% CI)	P value
Protein Malnutrition (any level)	1.54 (0.82–2.90)	0.18		
Pressure Ulcer (any stage)	6.20 (3.40–11.30)	<0.0001	3.48 (1.91–6.36)	<0.0001
Sepsis	5.05 (2.61–9.78)	<0.0001		
Urinary Tract Infection	1.94 (1.02–3.69)	0.04		
Diabetes (ever)	2.34 (1.30–4.20)	0.004		
Pneumonia	2.03 (1.14–3.64)	0.02		
Device				
Drainage Tubes	1.95 (1.09–3.50)	0.03	2.63 (1.38–4.98)	0.003
Enteral Tube Feeds	8.75 (3.46–22.12)	<0.0001	4.46 (1.74–11.43)	0.002
Dialysis	4.98 (2.78–8.90)	<0.0001	2.22 (1.15–4.27)	0.02
Indwelling Urinary Catheter	N/A[a]	N/A[a]		
Rectal Tube	4.12 (1.82–9.33)	0.0007		
Gastrointestinal-Feeding Tube	2.17 (1.19–3.95)	0.01		
Device Days (per 10 days)				
Drainage Tubes	1.33 (1.13–1.56)	0.0006		
Enteral Tube Feeds	1.09 (0.94–1.26)	0.24		
Dialysis	1.07 (0.87–1.30)	0.53		
Indwelling Urinary Catheter	1.45 (1.32–1.60)	<0.0001		
Rectal Tube	1.78 (1.02–3.08)	0.04		
Gastrointestinal-Feeding Tube	1.30 (0.90–1.88)	0.17		

Note. RR, risk ratio; CI, confidence interval; BMI, body mass index; ICU, intensive care unit; LOS, length of stay; *C. difficile*, *Clostridioides difficile*.
[a] Unable to calculate.

transmission was facilitated via carbapenemase gene *bla* VIM-1 insertion into a promiscuous plasmid [15]. Also, *bla* VIM-1 and *bla* VIM-2 genes were identified in a sink drain and environmental service cart, respectively [15]. These data may link CP-CRE transmission to an environmental source; however, the role of environmental reservoirs (e.g., sink drains) in CP-CRE transmission at KAMC remains unclear and requires further study.

Our results indicate that risk of CP-CRE acquisition was over 2 times greater for morbidly obese ICU patients compared to ICU patients who were not morbidly obese (RR, 2.10; 95% CI, 1.12–3.95). Only CP-CRE colonized patients were diagnosed as obese and morbidly obese. Also, morbid obesity was the only body mass index category independently associated with CP-CRE acquisition; overweight and obesity were not. Mechanisms responsible for the association between morbid obesity and CP-CRE acquisition are unclear; however, altered antibiotic pharmacokinetics, immunological changes, and changes to gut microbiota have been proposed [16–18].

Anecdotal data from staff at KAMC suggests that patients with severe obesity are difficult to clean due to multiple skin folds and difficulty in turning patients. Current hospital infection prevention measures should be evaluated for morbidly obese patients to identify gaps in practices for cleaning (e.g., daily baths) patients.

Our data indicate that ever being admitted to a medical ICU is an independent risk factor of CP-CRE acquisition (RR, 2.39; 95% CI, 1.32–4.35). A subgroup analysis shows that a higher proportion of medical ICU patients were morbidly obese, had more comorbidities, negative outcomes (i.e., diagnoses), antibiotics, and invasive devices. These were controlled for in the final multivariate regression analysis; however, these data suggest that the medical ICU population may have been more susceptible to CP-CRE acquisition compared to other ICU populations. The chronic levels of CP-CRE on medical ICU A compared to other medical ICUs may indicate that an environmental source or other factor played a role in CP-CRE transmission on this unit; however, environmental sampling and isolate typing were not performed.

Antibiotics are a primary risk factor for CP-CRE acquisition due to the selective pressures that antibiotics exert on bacteria [7]. Of the 11 types/classes of antibiotics assessed in this study, only carbapenem use in the prior 90 days (RR, 2.27; 95% CI, 1.21–4.26) was identified as an independent risk factor for CP-CRE acquisition in our study. This is supported in the literature and emphasizes the importance of antibiotic stewardship including carbapenems [7].

In our study, the risk of CP-CRE acquisition increased 3.5 times (95% CI, 1.27–9.68) with a diagnosis of *C. difficile* enterocolitis in the prior 90 days. Previous *C. difficile* infection has been identified as an independent risk factor for co colonization of CP-CRE and *C. difficile*; however, not for CP-CRE colonization alone [19]. *Clostridioides difficile* infections share similar risk factors to CP-CRE and other multidrug-resistant organisms including antibiotic usage, invasive devices/procedures, and chronic health conditions [19]. Indeed, the use of stool specimens submitted for testing for suggestive *C. difficile* infection has been proposed for active surveillance of CRE [20]. In our study, *C. difficile* was associated with multiple antibiotics, but unlike CP-CRE, was not associated with carbapenem usage. Hence, the association between *C. difficile* and CP-CRE is thought to be attributed to patients receiving antibiotics that were either not measured (i.e., prescribed as outpatient) or not included in our study.

The diagnosis of a pressure ulcer in the previous 90 days increased the risk of acquiring CP-CRE by nearly 3.5 times (95% CI, 1.91–6.36). This association has been reported in the literature [21]. Decreased mobility and chronic comorbidities are

considered risk factors for pressure ulcer development [22]. Anecdotal data at KAMC suggest that proper cleaning and bathing is more difficult with bedridden patients. This is important since exposure to CP-CRE may lead to colonization and daily bathing with antiseptic wipes (i.e., chlorhexidine gluconate) has been shown to reduce CP-CRE colonization when used as an element of infection prevention bundles [23].

The association between CP-CRE acquisition and enteral tube feeds and drainage tubes has been reported in the literature [24,25]. Enteral tube feeds were associated with the highest risk of CP-CRE acquisition in our study (RR, 4.46; 95% CI, 1.74—11.43). This association may be related to tube feed disruption of colon microbiota and reduction of gastric pH, which may facilitate pathogen colonization [26,27].

Associations between CP-CRE acquisition and dialysis has been observed in previous studies [28]. The effects of end stage renal disease (ESRD) on the immune system and gut microbiota may help explain the relationship between dialysis and CP-CRE acquisition. Renal failure is associated with an increase in urea levels in the blood, which impacts both the innate and adaptive arms of the immune system and leads to immunodepression [29]. Furthermore, increases in urea and uric acid as well as dietary restrictions of fruits and vegetables of ESRD patients shifts bacteria populations away from those associated with colonic fermentation, important in maintaining mucosal health, towards those that possess urease, uricase, and indole- and *p*-cresyl-forming enzymes [30].

This study has some limitations. A low number of CP-CRE positive patients were identified (*N*=48), which limits the ability to detect small measures of effect. There is also no certainty that all ICU patients in the study period were captured in the extracted medical records. We identified 3 CP-CRE positive patients that were not included in the data extraction, indicating that some patients without CP-CRE may not have been included as well. Nonetheless, this would be considered a random occurrence and the final cohort of 7,026 is an adequate representation of our study population.

In this study isolates were screened for carbapenemase activity with the MHT. The MHT is not as sensitive as other phenotypic and molecular methods and could have biased study results [31,32]. Also, the Nanosphere Verigene® system, was unavailable to confirm some CP-CRE isolates for carbapenemase genes. Hence, the incidence of KPC and VIM carbapenemases is likely higher in our study population. Lastly, we only assessed medications administered during a patient's hospital stay at KAMC and not at home or at other healthcare facilities.

Conclusions

In summary, we identified 8 independent risk factors of CP-CRE acquisition at KAMC. These included administration of enteral tube feeds; a diagnosis of *C. difficile* enterocolitis, pressure ulcer, and morbid obesity; presence of a drainage tube; admission to a medical ICU; exposure to a carbapenem; and dialysis procedure. To our knowledge, this is the first published study to identify independent risk factors of CP-CRE acquisition in a healthcare facility within the state of Kentucky. In addition, due to weekly CP-CRE surveillance and the retrospective cohort study design, this is one of few studies with published incidence densities of CP-CRE acquisition within a US healthcare facility. Most risk factors identified in this study

were associated with alteration of colon microbiota and invasive procedures, and have been reported in the literature. The exception is morbid obesity, which is absent from the literature to the authors knowledge. These data are useful in developing interventions to prevent CP-CRE and in implementing a more targeted CRE active surveillance program.

Credit author statement

Jason Wilson: Writing-original draft preparation, data curation, conceptualization. **Wayne Sanderson**: Project administration. **Kathleen Winter**: Methodology. **Phil Westgate**: Formal analysis. **Derek Forster**: Supervision, resources.

Conflicts of interest

All authors report no conflicts of interest relevant to this article.

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