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Carbapenem-Resistant Enterobacteriaceae (CRE): Epidemiology, Duration of Carriage, and Progression to Infection in a Large Healthcare System in Miami, FL

Adriana Jimenez
ejime005@fiu.edu

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FLORIDA INTERNATIONAL UNIVERSITY

Miami, Florida

CARBAPENEM-RESISTANT ENTEROBACTERIACEAE (CRE): EPIDEMIOLOGY, DURATION OF CARRIAGE, AND PROGRESSION TO INFECTION IN A LARGE HEALTHCARE SYSTEM IN MIAMI, FL

A dissertation submitted in partial fulfillment of

the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

PUBLIC HEALTH

by

Adriana Jimenez

2020

To: Dean Tomás R. Guilarte
Robert Stempel College of Public Health and Social Work

This dissertation, written by Adriana Jimenez, and entitled Carbapenem-Resistant Enterobacteriaceae (CRE): Epidemiology, Duration of Carriage, and Progression to Infection in a Large Healthcare System in Miami, FL, having been approved in respect to style and intellectual content, is referred to you for judgment.

We have read this dissertation and recommend that it be approved.

_____
Kristopher Fennie

_____
Boubakari Ibrahimou

_____
Kalai Mathee

_____
Silvia Munoz-Price

_____
Vukosava Pekovic

_____
Mary Jo Trepka, Major Professor

Date of Defense: November 9, 2020

The dissertation of Adriana Jimenez is approved.

_____
Dean Tomás R. Guilarte
Robert Stempel College of Public Health and Social Work

_____
Andrés G. Gil
Vice President for Research and Economic Development
and Dean of the University Graduate School

Florida International University, 2020

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DEDICATION

This dissertation is dedicated to my loved family, my partner in crime Steven Spahr, my beautiful daughter Nicole Spahr, my unconditional and selfless mother Beatriz Cardenas, and my best friend and true soul sister Magda Montano. Without your support, patience, and understanding through all these years this accomplishment wound never materialized. You hold my hand through cancer treatment and the stress of an unprecedent pandemic so I would not lose my north and keep working harder to reach my dreams.

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ABSTRACT OF THE DISSERTATION

CARBAPENEM-RESISTANT ENTEROBACTERIACEAE (CRE): EPIDEMIOLOGY, DURATION OF CARRIAGE, AND PROGRESSION TO INFECTION IN A LARGE HEALTHCARE SYSTEM IN MIAMI, FL

by

Adriana Jimenez

Florida International University, 2020

Miami, Florida

Professor Mary Jo Trepka, Major Professor

Carbapenem-resistant *Enterobacteriaceae* (CRE) are multidrug-resistant organisms (MDRO) considered by the CDC as an urgent public health threat that is spreading globally. Little is known about the epidemiology of CRE in Miami, FL. The purpose of this dissertation was to 1) Evaluate trends in the epidemiology of CRE among patients admitted to the acute care facilities of the largest healthcare system in Miami, FL between 2012 and 2016, 2) Identify factors associated with progressing to infection among patients colonized with carbapenemase-producing *Enterobacteriaceae* (CPE), and 3) Determine the duration of CPE carriage and factors associated with long-term carriage in our cohort.

A total of 371 CRE cases were identified retrospectively. The overall prevalence was 0.077 per 100 patient-admissions; the admission prevalence was 0.019 per 100 patient-admissions, and the incidence density was 1.46 cases per 10,000 patient-days. Rates increased during the first three years of the study and declined in the last two.

Of 54 patients colonized with CPE, 16 (30%) of them developed CPE infections. The mean time for infection development was 63 days. Cox regression analysis identified the use of an indwelling urinary catheter (HR 4.4; *P*-value=0.034), exposure to intravenous colistin (HR 3.2; *P*-value=0.037), and transfer from overseas facilities (HR 9.8; *P*-value=0.021) as variables associated with the development of infection. Additionally, out of 75 eligible patients, 25 (33%) were cleared from CPE-carrier status. Immunocompromised patients, those that had mechanical ventilation exposure, or exposure to carbapenems had a lower probability of being cleared from CPE-carrier status (HR 0.34; 0.34, and 0.14 respectively (*P*-value <0.05]). Having CPE isolated from >1 anatomical body site was associated with a 5.3 times higher probability of being cleared from CPE-carrier status (*P*-value <0.001). The median time for clearance was 80 days (Range 16-457).

In conclusion, the use of MDRO registries and active surveillance testing contribute to control increasing rates of CRE. Furthermore, infection prevention and antimicrobial stewardship interventions aimed to decrease unnecessary use of medical devices and rapid selection of effective treatment are key factors to prevent the development of CPE-related infections among CPE colonized patients as well as to prevent long-term CPE carriage.

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ABBREVIATIONS AND ACRONYMS

CAUTI	Catheter associated urinary tract infection
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CLABSI	Central line associated bloodstream infection.
CRE	Carbapenem Resistant *Enterobacteriaceae*
CR-KP	Carbapenem-resistant *Klebsiella pneumoniae*
CPE	Carbapenemase-producing *Enterobacteriaceae*
EMR	Electronic Medical Record.
FL-DOH	Florida Department of Health.
HAI	Hospital-acquired infections
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICU	Intensive care unit.
IM	Imipenase
KPC	*Klebsiella pneumoniea* carbapenemase
LTCF	Long-term-care facility
MDRO	Multidrug-resistant organism
NDM	New Delhi metallo-β-lactamase
Non-CP-CRE	No Carbapenemase producer carbapenem-resistant *Enterobacteriaceae*
NHSN	National Healthcare Safety Network
OXA	Oxacillinase
PCR	Polymerase chain reaction

SSI	Surgical site infection
VIM	Verona integron-encoded metallo-β-lactamase
US	United States

INTRODUCTION

Carbapenem-resistant *Enterobacteriaceae* (CRE) are Gram-negative bacilli that are resistant to carbapenems. Carbapenems are broad-spectrum antibiotics considered as the last resort for the treatment of *Enterobacteriaceae* infections.[1] The Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) classified CRE as an urgent threat that requires public health attention for treatment and prevention and a critical priority for research.[2,3] In 2019, the CDC estimated about 13,100 infections by CRE and about 1,100 deaths in the United States.[3] The most common species of CRE in the US are *Klebsiella pneumoniae, Enterobacter aerogenes/cloacae,* and *Escherichia coli* with reports of 5.7 %, 4.8 %, and 0.6 % of them being carbapenem-resistant respectively.[3,4] Most of the CRE cases in the US are reported from the East-North-Central, Mid-Atlantic, and South-Atlantic areas.[4] CRE infections are associated with increased morbidity, mortality, and extended hospital length of stay (LOS).[1,3,5-7]

CRE are not among the reportable diseases/conditions in Florida.[8] Therefore, there are limited data about the incidence of CRE in Miami-Dade County. CRE have been described in Florida since 2008 but mainly during various outbreaks.[9-11] Miami-Dade County is constantly receiving visitors and immigrants from different parts of the world known to be endemic with CRE; [6,12] this poses a high risk for the spread of CRE in the South Florida community. According to the CDC's Antibiotic Resistance & Patient Safety Portal, the CRE estimate for select healthcare-associated infections (HAIs) is 2.7% for the US and 2.1% for Florida for the period of 2011 to 2018.[4] This percentage is based on only three HAI types reported to the CDC (Central line associated bloodstream infection [CLABSI], catheter associated urinary tract infection [CAUTI], surgical site

infection [SSI]). The report excludes isolates from other HAIs, as well as community-acquired conditions, and isolates from active surveillance testing; therefore it does not reflect the total burden of CRE in the US.[4]

Carbapenem-resistant *Enterobacteriaceae* (CRE) can be resistant to carbapenems by different mechanisms including augmented drug efflux, a mutation in or loss of outer membrane porins, and production of carbapenemases.[6,13,14] Carbapenemases are a type of β-lactamases that breakdown carbapenems, making the treatment with this class of antibiotics ineffective. Although CRE poses a challenge for the patient's antibiotic therapy, carbapenemase-producing *Enterobacteriaceae* (CPE) present a bigger problem for infection prevention, and treatment, since carbapenemase production is frequently plasmid-mediated; plasmids give the microorganism the capability to transfer genetic information for carbapenems resistance to other species of Gram-negative bacilli (i.e. other *Enterobacteriaceae*, *Pseudomonas* or *Acinetobacter).*[14] In 2017 Tamma et al., reported that the odds of dying among patients that developed bloodstream infection (BSI) by CPE are five times higher compared to those with BSI caused by non-CPE.[15] Since the first reports in the early 1990s, CPE has spread across the world.[6,7,14]

There are four classes of β-lactamases associated with carbapenem resistance: A, B, C, and D. Classes A, C, and D are serine enzymes, and class B includes metalloenzymes. This differentiation is important because metallo-β-lactamases are not inhibited by avibactam; combinations of avibactam are currently used to treat CPE infections.[16] In class A, *Klebsiella pneumoniae* carbapenemase (KPC) is the most important; KPC enzyme production is plasmid-mediated and considered endemic in the United States, Argentina, Brazil, Colombia, Italy, Greece, Israel, and China.[6,7,14,17-19] Class A also

includes the less common Guiana extended-spectrum β-lactamase (GES), and *Serratia marcescens* enzyme (SME). Class B carbapenemases are metallo-β-lactamases (MBLs) and include imipenemase (IMP), Verona integrin-encoded MBL (VIM), and New Delhi MBL (NDM); class B carbapenemases are more common in certain areas of Asia and Europe; nevertheless, there have been case reports and sporadic outbreaks across several states in the US caused by organisms carrying these carbapenemases.[6,16] Class C includes ampC, CMY, and ACT; these carbapenemases are less common. Finally, class D carbapenemases are plasmid-mediated oxacillin-hydrolyzing β-lactamases; OXA 23, OXA-48, and OXA-58 are the most frequently found. OXA-48 is considered endemic in some Mediterranean countries such as Turkey, France, and Spain; there have been case reports and sporadic outbreaks reported throughout the United States.[6,16,20]

Previous studies have assessed risk factors associated with infection and carriage with CPE among pediatric and adult populations identifying risk factors for special populations such as neonates, solid organ transplant recipients, and oncology patients, among others. These risk factors include admission to intensive care units (ICU), use of invasive devices such as ventilators, comorbidities, invasive procedures, exposure to hospital care, CPE exposure, solid organ transplant, living in long term care facilities, and antibiotic exposure.[21-23] One important risk factor identified in several studies for CPE infection is previous colonization with these organisms; CPE colonization increases the odds up to ten times for developing systemic infections caused by CPE.[24] Moreover not all patients who acquire CPE develop infections by these organisms, with many remaining only colonized.[24-27] A recent systematic review found that, overall, 16% of patients colonized with CRE develop infections.[28] Most studies in the US are related to

the acquisition of CRE/CPE or the development of infection among at-risk populations.[5,17,23,29-32] There are few studies assessing variables associated with progression to infection among adults colonized in the acute care setting.[28] One study among a pediatric population found that underlying metabolic disease, previous carbapenem exposure, neutropenia, and previous surgical procedure are independent risk factors for carbapenem-resistant *Klebsiella pneumoniae* (CR-KP) infection in patients previously colonized with the same organism.[33] Most studies related to colonization with CPE are from Israel or Europe, and their results cannot necessarily be extrapolated to the US due to differences in antibiotic use, practices, and prevalent carbapenemase.[28] Furthermore, most of these studies address questions related only to *Klebsiella pneumoniae* leaving a gap in knowledge for other species of *Enterobacteriaceae.* There are limited data available that allow identification of factors associated with the development of clinical infection by CPE in patients colonized by the same organism in the US. The few reports are limited to rectal colonization, leaving a knowledge gap about factors associated with infection due to colonization in other body sites.[25,26]

In 2015 the CDC issued a toolkit with recommendations for healthcare facilities to prevent and control the spread of CRE.[1] These recommendations include monitoring and promoting hand hygiene compliance, placing CRE patients on contact precautions (CP), staff education, minimizing the use of devices, timely notification by the laboratory, inter-facility communication for patient transfers, establishing antimicrobial stewardship programs, daily environmental cleaning of areas nearby of the patient, patient and staff cohorting using dedicated staff for CRE patients, screening contact of CRE patients, active surveillance testing particularly high-risk populations, and chlorhexidine (CHG)

bathing.[1] Unfortunately, CDC recommendations do not provide guidance on how long a patient, either colonized or infected with CRE/ CPE, should be placed in CP to prevent horizontal transmission in acute care facilities; there is not enough evidence yet to make such recommendations,[1] leaving it up to the facility to determine how long to maintain CP for these patients during index admission and readmissions. Placing patients on CP indefinitely with dedicated staff places an extra burden on the facility. Few studies have assessed the duration of carriage of CPE, most of them in Israel.[27,34-38] There is limited research about this topic in the US. Recently, the Society for Healthcare Epidemiology of America (SHEA) published an expert guidance for duration of CP for acute-care facilities that includes CP for CRE among other multidrug resistant organisms; this expert guidance was based on a systematic review and a survey distributed among the SHEA research network.[39] In the systematic review, the authors found wide variability on median time for carriage clearance. Again, most studies included in the review were from Israel, China, or Europe. In the SHEA survey, only 32% of the facilities reported having policies that allow discontinuation of CP for CRE; 28% reported using screening tests for discontinuing CP; 38% reported using a 'greater than 1 year since last positive test' rule to discontinue CP. The expert guidance recommends maintaining CP indefinitely for extensively drug-resistant *Enterobacteriaceae* such as CP-CRE.[39] More recently, the European Centre for Disease Prevention and Control published their expert guidance for infection prevention control and management of CRE in healthcare facilities;[40] this guidance recommends to discontinue contact precautions on patients with history of CRE carriage on a case-by-case assessment based on patient risk factors for prolonged carriage.[40]

In conclusion, little is known about the epidemiology of CRE in Miami-Dade County, as well as factors associated with the development of CPE-related infections among those previously colonized, or when is appropriated to discontinue CP for patients with a history of CPE-carriage.

The overall aim of this dissertation was to evaluate trends in the epidemiology of CRE and CPE among patients admitted to acute care facilities of Miami-Dade County. We also aimed to identify risk factors associated with the development of CPE-related infections among previously colonized patients and to evaluate the median duration of CPE carriage and identify factors related to a long-term carriage. We conducted three retrospective cohort studies among patients admitted to any of the acute care facilities of the largest healthcare system in Miami-Dade County between 2012-2016. This dissertation contributes to the field by providing information for public health authorities and the healthcare community in Miami-Dade County about possible unrecognized trends in antimicrobial resistance in the community through incidence density rate of CRE and CP-CRE; identification of populations at risk for CPE infection in the community, and a baseline for guidance for infection control management of CPE carriage in acute care settings not only in Miami-Dade County, but also across the US and other areas in the world with similar CRE epidemiology.

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Epidemiology of carbapenem-resistant Enterobacteriaceae in hospitals of a large healthcare system in Miami, Florida from 2012 to 2016: Five years of experience with an internal registry

Abstract

Background: Carbapenem-resistant Enterobacteriaceae (CRE) is an urgent public health threat globally. Limited data are available regarding the epidemiology of CRE in South Florida.

We describe the epidemiology of CRE within a large public healthcare system in Miami, FL, the experience with an internal registry, active surveillance testing, and the impact of infection prevention practices.

Methods: Retrospective cohort study in four hospitals from a large healthcare system in Miami-Dade County, FL from 2012 to 2016. The internal registry included all CRE cases from active surveillance testing from rectal/tracheal screening occurring in the ICUs of two of the hospitals and clinical cultures across the healthcare system. All CRE cases were tagged in the electronic medical record and automatically entered into a platform for automatic infection control surveillance. The system alerted about new cases, readmissions, and transfers.

Results: A total of 371 CRE cases were identified. The overall prevalence was 0.077

cases per 100 patient-admissions; the admission prevalence was 0.019 per 100 patient-admissions, and the incidence density was 1.46 cases per 10,000 patient-days. Rates increased during the first three years of the study and declined later to a lower level than at the beginning of study period.

Conclusion: Active surveillance testing and the use of an internal registry facilitated prompt identification of cases contributing to control of increasing rates of CRE by rapid implementation of infection prevention strategies.

Background

Carbapenem-resistant *Enterobacteriaceae* (CRE) are an urgent public health threat because of their current rapid spread around the world, and high morbidity and mortality.[1,2] The Centers for Disease Control and Prevention (CDC) estimates that there are approximately 13,100 new infections and approximately 1,100 deaths by CRE over time from 2012 -2017.[1] Recent publications estimate that the CRE incidence in the US ranges between 0.46 and 4.17 cases per 10,000 patient-days,[3] and it is more prevalent in highly populated areas such as California, Chicago, and New York.[4-6] Risk factors for CRE acquisition have been extensively described and include the presence of medical devices, prolonged stay in healthcare facilities, surgery, antibiotic exposure, solid organ transplant, and travel to endemic areas.[1,7] Among the different mechanisms for carbapenem resistance, carbapenemase production is of major concern because it spreads easily, as it is frequently plasmid-mediated; genetic information can be shared among different bacterial species by this mechanism.[7-9]

Despite recent efforts, little is known about the epidemiology of CRE in South Florida, in part because these organisms are not reportable in the state.[10] Therefore, there are limited data about the burden of CRE in the region, although cases have been sporadically described in the state since 2008.[11-13] According to the CDC in Florida, 2.5% of the *Enterobacteriaceae* related to healthcare-associated infections (HAI) are CRE.[14] This percentage is based on central line-associated bloodstream infections, catheter-associated urinary tract infections, and surgical-site infections; it excludes isolates from other HAI, as well as community-acquired infections, and isolates from active surveillance testing.[14] The Florida Department of Health (FL-DOH) has developed collaborative efforts for CRE surveillance and prevention;[15] one of them found carbapenem-resistant *Klebsiella pneumoniae* (CR-KP) incidence density of 0.473 per 10,000 patient-days in 2014 (unpublished data). The study also indicated that Miami-Dade County facilities had higher CR-KP incidence than facilities from other counties. Additionally, since 2014, FL-DOH requires all laboratories participating in the electronic laboratory reporting (ELR) to submit the susceptibility testing results of *Klebsiella* species, *Escherichia coli*, *Enterobacter* species, *Citrobacter* species, and *Serratia* species from sterile sites;[16] moreover, participation in ELR is not mandatory. The use of statewide CRE registries has been recently reported to contribute to the control of CRE spreading by tracking patients who are carrying these organisms and notifying the admitting healthcare facility so proper infection prevention precautions can be started timely.[17,18]

Miami-Dade County is the seventh-largest county in the US and regularly receives visitors and immigrants from different parts of the world known to have endemic

CRE such as Venezuela, Brazil, and Colombia.[7,19] Thus, South Florida is one of the main entry points in the US for CRE from South America making the understanding of its epidemiology of great importance. Currently neither the state of Florida nor Miami-Dade County count with a state wide CRE registry. Here we aimed to describe the epidemiology of CRE comparing carbapenemase-producing CRE (CP-CRE) versus non-carbapenemase-producing carbapenem-resistant *Enterobacteriaceae* (Non-CP-CRE) in four hospitals of a large healthcare system in Miami-Dade County and the experience using an internal registry for patients carrying CRE .

Methods

Setting

This was a retrospective cohort study of patients admitted to hospitals of a large health care system in Miami-Dade County between January 2012 and December 2016. The health system has over 2,000 licensed beds; it is composed of four hospitals. Facility A is a 1,100-bed major-teaching hospital with 134 adult intensive care unit (ICU) beds; this facility is associated to the University of Miami, and it is also a national and international referral center providing services in several specialties including one of the largest transplant programs in the US. Facility B is a 358-bed community hospital with 62 ICU bed, that serves the northern area of the county; it receives admissions mainly from surrounding long-term-care facilities (LTCF). Facility C is a 200-licensed bed community hospital with 26 ICU beds and serves the southern area of the county; it receives fewer admissions from nearby LTCF compared to Facility B. Lastly, Facility D is a 325 licensed-bed major-teaching children hospital with 156 ICU beds, is associated

to the University of Miami, and is a referral center offering a wide range of services including transplant. This study was approved by the Institutional Review Board of Florida International University.

Data collection

CRE cases were identified as part of the daily operation of the infection control department and entered into a database. Only the first CRE isolate per patient in any specimen source was included in the calculation of rates, this way each patient was counted only once. Data were collected from the patient's electronic medical record (EMR) and the infection control automatic surveillance system (Vigilanz©). In addition, the total number of *Enterobacteriaceae* tested against carbapenem and the number reported as resistant were obtained from the automatic surveillance system.

Variable definitions

Carbapenem-resistant *Enterobacteriaceae* (CRE) were defined as *Enterobacteriaceae* isolates reported resistant to any of the carbapenems listed by the Clinical and Laboratory Standards Institute (CLSI) guidelines or that tested positive for carbapenemase production from any specimen source.[20] CRE cases were defined as those where CRE carriage was identified via clinical or surveillance cultures. Carbapenemase-producing CRE (CP-CRE) were defined as *Enterobacteriaceae* isolates with carbapenemase detected by any method. Non-carbapenemase-producing carbapenem-resistant *Enterobacteriaceae* (Non-CP-CRE) were those CRE with carbapenemase test results reported as not detected. Cases were classified as community-onset if the specimen was collected ≤3 days after admission or hospital-onset if the

specimen was collected >3 days after admission. Secondary outcomes included 30-day mortality where day 1 was the day of the first positive CRE culture.[19]

Infection prevention interventions

In addition to the NHSN requirements for HAI surveillance, [20] beginning 2009, surveillance for CRE has been in place at all the facilities within the healthcare system. Rectal surveillance cultures and tracheal aspirates (ventilated patients) were collected on admission/transfer to the ICUs and weekly thereafter in Facility A; this strategy was expanded to the ICU of Facility B in 2014. Compliance with the surveillance culture collection protocols was monitored as point prevalence at different points of the study period. In 2010 a database for CRE was created and updated manually. In 2011 a new electronic platform for infection control surveillance was made available to the department; this platform was fed real-time with patient demographics and results from the EMR via an interface and enabled automatically updates to the internal CRE database.

In all the facilities, patients with CRE were placed on contact precautions for the duration of their admission. If readmitted, patients with Non-CP-CRE were placed in contact precautions for up to two years from the last positive culture; patients with CP-CRE were placed in contact precautions in all readmissions. For each patient, the EMR was tagged indicating that the patient needed contact precautions; this tagging was visible in all pages of the EMR and was only discontinued by the Infection Control Department. Contact precaution for CRE included private room setting, staff cohorting, use of gown and gloves as per contact precautions. Compliance with isolation precautions was

monitored by the Infection Control Department during daily rounds. Additionally, the surveillance system was set up to alert the Infection Control Department about new CRE isolates and known CRE cases readmissions. If carbapenemase production was detected, the unit leadership hosting the patient was notified immediately via phone call and email by the infection preventionist covering the unit, and cohorting of staff and patients was initiated. Daily environmental disinfection was done using bleach-based products; from 2009 to 2014 environmental cleaning was routinely monitored using UV markers as previously described.[21] In August 2014, in response to an increased number of CP-CRE cases, the infection control department started emailing the daily list of all CP-CRE patients currently in the facility to bed placement, nursing unit leadership, environmental services, antimicrobial stewardship, and respiratory therapy to facilitate patient and staff cohorting.

In early 2015, Facility A experienced an outbreak of *Klebsiella pneumonia*e carbapenemase (KPC)–producing *Citrobacter freundii* in one of its ICUs. As previously reported, in response to the outbreak, the staff of the ICU received infection prevention education; at the same time, the unit went into plumbing repairs.[13] In addition to the above-mentioned interventions, the system participated in the FL-DOH CRE initiatives, which provided education and expert support.

Microbiology testing

Surveillance cultures for CRE were performed by perirectal swab or tracheal aspirate sample cultured on a MacConkey plate with meropenem and ertapenem disks followed by full identification and susceptibility testing as previously described.[12] CRE

isolates were routinely frozen for long-term storage. Identification and susceptibility testing for clinical and surveillance cultures were performed using Vitek2 and confirmed by E-test; if deemed resistant to any carbapenem, the isolate was further tested for carbapenemase production. There were no changes in the methodology for antimicrobial susceptibility testing during the study period. From 2012 to 2014 carbapenemase production was tested using the Modified-Hodge-test; starting in 2015 carbapenemase test was done using CarbaNP test.[22] No further testing was routinely performed. In addition, the isolates associated with the KPC-*Citrobacter* outbreak in 2015 were sent to the University of Pittsburgh for molecular testing,[13] and the frozen isolates underwent further molecular testing later as part of this study.

Molecular testing

Crude DNA was prepared by the boiling method and used as the template for polymerase chain reaction (PCR). Multiplex PCR was performed to detect bla_{KPC}, bla_{NDM}, bla_{OXA-48}, as described previously.[23] For *S. marcescens*, a separate PCR was performed to detect bla_{SME}, also as previously described.[24]

Pulsed-field gel electrophoresis (PFGE) analysis was performed using restriction enzyme XbaI (New England Biolabs, Ipswich, MA) and a CHEF III DR electrophoresis system (Bio-Rad, Hercules, CA). The relatedness of PFGE patterns was determined by the unweighted-pair group method using average linkages and cluster analysis with the Dice setting on Bionumerics software (Applied Maths, Sint-Martens-Latem, Belgium).

Statistical analysis

Facility-specific rates were calculated following the CDC definitions: Incidence density rate was calculated dividing the number of new hospital-onset cases by total number of patient- days and multiplying by 10,000. Admission prevalence was obtained dividing the number of CRE community-onset events by the number of patient admissions and multiplying by 100. Overall admission prevalence was calculated dividing the number of first CRE cases (regardless of time spent in the facility) by the number of patient admissions and multiplying by 100. Percent of CRE was calculated by dividing the total number CRE by the number of *Enterobacteriaceae* tested for carbapenem susceptibility and multiplying by 100.[20]

Non-CP-CRE and CP-CRE subgroups and rates were compared using t-tests for continuous measures and $\chi 2$ or the Fisher exact test for categorical measures. Statistical analyses were conducted using SPSS version 26 software (IBM, Armonk, NY). *P*-values <0.05 were considered statistically significant.

Results

Demographics

From 2012 to 2016, a total of 371 unique CRE cases were identified. Of these, 160 (43%) had Non-CP-CRE, 150 (40%) had CP-CRE, and 61 (16%) were not tested for carbapenemase production (Table 1). The largest proportion of cases was among males (58%), Black/Non-Hispanics (45%) followed by White/Hispanics (34%), and among patients $\geq$ 65 years old (46%). Mortality within 30 days after identification of the first CRE isolate was 21%. There was no significant difference in the crude mortality rate at

30 days (P = 0.51) between CP-CRE and Non-CP-CRE cases. Overall, 280 cases were hospital-onset (75%) and 91 were community-onset (25%). An examination of the 91 community-onset cases revealed that all had previous exposures to healthcare-facilities; furthermore, 17 (19%) were transferred from a hospital in South-Florida not associated with our health system, 33 (36%) were transferred from LTCF, 33 (36%) were admitted from their homes but had previous exposures to healthcare-facilities in the previous 6 months, and 8 (9%) were international patients from Nicaragua, Ecuador, Bahamas, Iran, and Turkey.

Microbiology

The most frequent source for CRE was urine (32%) followed by respiratory tract (29%) [Table1]. Only 16% of CRE cases were detected first by rectal surveillance cultures. *Klebsiella pneumoniae* and *Enterobacter cloacae* were the most frequent CRE species identified, 50% and 14% respectively. Out of the 371 cases, 30 patients had more than one CRE species isolated with a maximum of 4 different species in one particular patient; these were collected in most cases from the same sources during the same admission. In total 132 CRE isolates were available for molecular testing; of those, 93 were positive by PCR for carbapenemase gene detection. The bla_{KPC} gene was detected in 84 (90%) of the isolates. Five (5%) of the isolates were positive for bla_{NDM} (New Delhi Metallo-β-lactamase); three of them were from international patients or recent travelers to Turkey,[25] Cuba, and the Bahamas; the other two cases were local patients. Most of the first isolates per case were resistant to piperacillin-tazobactam (96%), aztreonam (96%),

cefazolin (97%), ceftriaxone (91%), and meropenem (92%) but susceptible to amikacin (87%) (Table 2).

During the study period, 47,963 *Enterobacteriaceae* isolates were tested against any of the carbapenems from all hospitals; 2.0% were reported as resistant to at least one carbapenem. (Table 3).

Rates of CRE

From 2012 to 2016, our health system had 484,602 patient admissions contributing 1,922,425 patient days. Overall prevalence, admission prevalence, and incidence density rate did not change significantly at the end of the study compared to 2012. The overall prevalence of CRE for all facilities combined was 0.077 cases per 100 patient admissions (95% confidence interval [CI], 0.069 – 0.085); the overall prevalence for Facility A was twice that of the three other facilities combined, while facility C had the lowest one for the system (Table 4). The CRE admission prevalence of all facilities combined was 0.019 per 100 patient admissions (95% CI, 0.015 - 0.023). The CRE incidence density of all facilities was 1.46 per 10,000 patient days (95% CI, 1.29 – 1.64). Facilities A and B had more than twice the incidence density than facilities C and D. The incidence density for CR-KP was 7.69 per 10,000 patient days (95% CI, 6.5 – 9.0); this result was significantly higher than the one found for the state during the 2014 FL-DOH collaborative of 0.47 per 10,000 patient-days (P = 0.003).

The overall prevalence and incidence density increased from 2012 to 2014 and then declined from 2015 to 2016; the maximum peaks were between March 2015 and June 2015 (Figure 1). These peaks were driven by a polyclonal cluster of KPC-producing

Klebsiella pneumoniae and a KPC-producing *Citrobacter* outbreak in Facility A.[13] The introduction of active surveillance testing in Facility B in 2014 was also responsible for the apparent increase of the incidence density in 2014 (Figures 1 and 2). The admission prevalence in Facilities A and B increased over the study period, even though the difference between the prevalence in 2012 compared to that of 2016 was not statistically significant (P = 0.7). During the study period, there were in total of 33,737 admissions to the units collecting surveillance cultures; 25,290 of them were screened at least once during the ICU admission (75% compliance).

Discussion

We describe the epidemiology of CRE within a large healthcare system in Miami-Dade County. In this cohort, we found similar distributions of the CRE isolates for source, species, and mechanisms of resistance as those previously reported in other highly populated areas of the US being *Klebsiella pneumoniae* the most frequent CRE found and urine the most common source. [3,5,14,26] Previous to our study, there were no data available about CRE rates among the Miami-Dade population. We believe this information is important when considering allocating resources at the regional level for CRE prevention as part of the CDC's HAI Prevention Program and providing a baseline for future strategic planning. Miami-Dade County is one of the most populated counties in the US and a port of entry for immigrants, visitors, and international patients from areas with endemic CRE.[8,18, 24]

The incidence of CRE in our facilities steadily increased during the first three years of the study. Nevertheless, after implementing several interventions aimed at

increasing early detection of cases, compliance with contact precautions, and environmental disinfection, the rates rapidly decreased to levels lower than at the beginning of the study. Early detection of cases by screening cultures of ICU patients and the use of an internal registry integrated with our surveillance system and EMR enabled rapid identification of new cases and readmissions. This information remained available across different admissions and transfers among in-network facilities. At the same time, tagging the EMR facilitated immediate initiation of specific precautions for CRE cases particularly among readmissions.

Our study shows that CRE is still uncommon in the pediatric and the community-hospital population in the southern area of the healthcare system. This is probably because the patients at these two facilities generally do not present from LTCF and do not have previous exposures to other healthcare-facilities. Furthermore, we did not identify any community-associated cases without known risk factors for CRE; all community-onset cases had previous exposures to healthcare-facilities or recent international travel. This finding suggests that during the study period, in Miami-Dade, CRE was confined to healthcare settings and was not spread in the community as has been document in other areas such as North Carolina, South Carolina, Virginia, India, Spain, and Argentina.[27]

After performing molecular testing on the saved isolates, we found five cases associated with CP-CRE harboring *bla*$_{\text{NDM}}$. Three of these cases were unnoticed during the patients' admissions, and they were "assumed" to be KPC producers as we did not have molecular diagnostics available. Not knowing the specific mechanism of carbapenemase production has serious implications for antimicrobial stewardship as the

treatment might be inappropriate based on the spectrum of activity of each agent and the need for combination therapy for metallo-β-lactamases. [28]

The study found an incidence density of CR-KP notably higher than the one found among participating facilities in the 2014 FL-DOH CRE collaborative (7.69 vs 0.47 cases per 10,000 patient days). Different from the FL-DOH collaborative, our study included surveillance cultures instead of relying exclusively on clinical cultures; relying only on clinical cultures reveals only the "tip of the iceberg" excluding the potential threat of CRE spread by cases. Recent studies have highlighted the importance of detecting cases to reduce the burden of CRE.[29] One strategy to increase detection of cases is to perform surveillance cultures in patients with known risk factors. According to a model recently developed by Bartsch et al. to explore the impact of increasing CRE carriers detection,[29] we estimate that 5.74 new cases were prevented by active surveillance testing by the end of 2016. This is taking into account that in 2016 active surveillance testing was already in place for 7 years, and we detected 1 out of 6 of the cases first by surveillance culture. In 2014 we expanded active surveillance testing and also increased the effectiveness of contact precautions using daily email notification to key personnel and education.

This study has several limitations. Not all patients were screened upon admission to the facility. Therefore, there is a possibility that some cases classified as hospital-onset were colonized on admission but only detected later during their admission and misclassified as hospital-onset. There is also the possibility that they were undetected because surveillance cultures were only done in the ICUs of the two larger facilities.

Furthermore, the screening method used was not highly sensitive, and compliance with surveillance cultures in the ICUs was only 75%. Screening every patient by culture upon admission in a system as large as ours would be costly; moreover, only screening ICU patients leaves out a large population of patients with known risk factors present on admission that are not admitted to the ICU. Hospitals considering implementing active surveillance cultures should take into consideration their influx of patients with risk factors for CRE who are not admitted to the ICU.

Unfortunately, our registry has the limitation of only being available to our network of facilities, and communication of CRE status to and from out-of-network facilities relied on manual documentation and was subject to human error. Recent reports indicate that the use of regional registries is effective in controlling the spread of CRE.[18,30,31] In our case, the internal registry played an important role in controlling the initially increasing CRE rates. Having a county-wide or state-wide registry would have a greater impact in the regional efforts to control the spread of CRE.[31] We urge state and local public health authorities to implement a regional registry to facilitate timely, accurate communication between healthcare facilities to ensure that when a patient with a history of highly drug-resistant organisms is admitted, prompt, appropriate infection prevention practices and targeted antimicrobial stewardship management can be implemented. In addition, it is important to differentiate CP-CREs vs non-CP-CREs as the mechanism of resistance and transmission are different, and hospitals need to cohort patients appropriately. Facilities with a similar prevalence of CRE as our institutions should consider routine testing of carbapenemase types to determine the specific mechanism of carbapenemase production taking advantage of available technologies.

Conclusion

In conclusion, our study demonstrated that the burden of CRE in our population of patients from Miami-Dade is similar to that of other highly populated cities in the US. Rising rates of CRE can be controlled by infection prevention strategies supported by tools such as registries and testing that allow rapid detection of carries and early interventions.

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Table 1. Patient with CRE characteristics in a large healthcare system in Miami-Dade County; 2012 - 2016.

		Non-CP-CRE n= 160	CP-CRE n= 150	CRE CPUnk n=61	All CRE n= 371	χ^2 p-value
Gender	Male	88 (55%)	86 (57%)	43 (70%)	217 (58%)	0.1052
	Female	72 (45)	64 (43%)	18 (30%)	154 (41%)	
Age (years)	≤ 17	14 (9%)	6 (4%)	4 (7%)	24 (6%)	0.3662
	18-44	21 (13%)	32 (21%)	11 (18%)	64 (17%)	
	45-64	52 (33%)	45 (30%)	16 (26%)	113 (30%)	
	≥ 65	73 (46%)	67 (45%)	30 (49%)	170 (46%)	
Race/ethnicity	White/Hispanic	51 (32%)	52 (35%)	22 (36%)	125 (34%)	0.2804
	White/Non-Hispanic	47 (29%)	36 (24%)	9 (15%)	92 (25%)	
	Black/Hispanic	4 (3%)	3 (2%)	1 (2%)	8 (2%)	
	Black/Non-Hispanic	53 (33%)	50 (33)	28 (46%)	131 (35%)	
	Other	0 (2%)	5 (3%)	1 (2%)	6 (2%)	
	Unknown	5 (3%)	4 (3%)	0 (0%)	9 (2%)	
LOS days, median (IQR)		37 (65)	48 (79)	44 (80)	48 (79)	0.2800
LOS to onset days, median (IQR)		16 (24)	18 (38)	13 (42)	19 (40)	0.2100
Facility	A -Major-teaching hospital	106 (66%)	117 (78%)	27 (44%)	250 (67%)	<0.001
	B - Community hospital	33 (21%)	20 (13%)	25 (41%)	78 (21%)	
	C - Community hospital	5 (3%)	7 (5%)	5 (8%)	17 (5%)	
	D - Major-teaching children hospital	16 (10%)	6 (4%)	4 (7%)	26 (7%)	
Mechanism of resistance	KPC	N/A	84 (90%)	N/A	84 (90%)	n/a
	NDM	N/A	5 (5%)	N/A	5 (5%)	

	OXA-48	N/A	1 (1%)	N/A	1 (1%)	
	SME	N/A	3 (3%)	N/A	3 (3%)	
Onset	HO	125 (78%)	116 (77%)	22 (36%)	280 (75%)	0.0712
	CO	35 (22%)	34 (23%)	39 (64%)	91 (25%)	
Organism	*Klebsiella pneumoniae*	81 (51%)	90 (60%)	16 (26%)	187 (50%)	0.0001
	Enterobacter cloacae	29 (18%)	15 (10%)	8 (13%)	52 (14%)	
	Escherichia coli	22 (14%)	13 (9%)	11 (18%)	46 (12%)	
	Enterobacter aerogenes	9 (6%)	6 (4%)	5 (8%)	20 (5%)	
	Serratia marcescens	6 (4%)	8 (5%)	6 (10%)	20 (5%)	
	Citrobacter freundii	2 (1%)	9 (6%)	2 (3%)	13 (4%)	
	Proteus mirabilis	4 (2%)	0 (0%)	5 (8%)	9 (2%)	
	Other	7 (4%)	7 (5%)	8 (13%)	22 (6%)	
Source	Surveillance culture rectal	35 (22%)	25 (17%)	1 (2%)	61 (16%)	0.0818
	Surveillance culture tracheal asp	0 (0%)	3 (2%)	0 (0%)	3 (0.8%)	
	Urine	49 (31%)	44 (29%)	25 (41%)	118 (32%)	
	Respiratory (clinical)	41 (26)	44 (29%)	24 (39%)	109 (29%)	
	Blood	13 (8%)	14 (9%)	4 (7%)	31 (8.3%)	
	Wound/drain	10 (6%)	11 (7%)	4 (7%)	25 (7%)	
	Other	12 (8%)	9 (6%)	3 (5%)	24 (6%)	
Expired within 30 days from first CRE isolate		38 (24%)	31 (21%)	10 (16%)	79 (21%)	0.4759

CRE carbapenem resistant *Enterobacteriaceae*; Non-CP Carbapenem resistant *Enterobacteriaceae* not-carbapenemase producer; CP-CRE, carbapenemase-producer carbapenem-resistant *Enterobacteriaceae*; CRE CPUnk, carbapenem resistant *Enterobacteriaceae* not tested for carbapenemase; LOS, length of stay; IQR, interquartile range; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA-48, oxacillynase-48; SME, *Serratia marcescens* enzyme; CO, community onset; HO, hospital onset.

Table 2. Susceptibility Profiles of Carbapenem-Resistant *Enterobacteriaceae* Isolates in a large healthcare system in Miami-Dade County, 2012-2016.

	Number of isolates (%)								
	Non-CP-CRE			**CP-CRE**			**All CRE**		
	S	**I**	**R**	**S**	**I**	**R**	**S**	**I**	**R**
Pip-Tazo	4 (3)	2 (2)	111 (95)	0 (0)	0 (0)	108(100)	6 (2)	4 (2)	245 (96)
Aztreonam	2 (8)	0 (0)	22 (92)	0 (0)	0 (0)	14 (100)	2 (4)	0 (0)	44 (96)
Cefazolin	1 (1)	0 (0)	90 (99)	0 (0)	0 (0)	79 (100)	7 (3)	0 (0)	213 (97)
Cefepime	5 (20)	2 (8)	18 (72)	5 (22)	5 (22)	13 (57)	24 (34)	8 (11)	39 (55)
Ceftazidime	11 (7)	3 (2)	142 (91)	6 (4)	7 (5)	131 (91)	31 (9)	14 (4)	316 (88)
Ceftriaxone	8 (5)	0 (0)	149 (95)	4 (3)	0 (0)	141 (97)	29 (8)	3 (1)	331 (91)
Ciprofloxacin	12 (48)	3 (12)	10 (40)	4 (20)	0 (0)	16 (80)	28 (42)	3 (5)	35 (53)
Levofloxacin	50 (32)	10 (6)	98 (62)	38 (26)	14 (10)	94(64)	112(31)	29 (8)	224 (61)
Meropenem	1 (0.6)	4 (2.5)	154 (96.9)	0 (0)	2 (1)	144 (99)	0 (0)	28 (8)	338 (92)
Amikacin	139 (88)	2 (1)	17 (11)	123 (84)	1 (1)	22 (15)	319 (87)	5 (1)	41 (11)
Gentamicin	87 (55)	6 (4)	64 (41)	72 (49)	12 (8)	62 (42)	197 (54)	22 (6)	145 (40)
Tobramycin	72 (46)	15 (9)	71 (45)	37 (25)	25 (17)	84 (58)	145 (40)	47 (13)	173 (47)
Trimethoprim	62 (39)	0 (0)	95 (61)	50 (34)	0 (0)	95 (66)	137 (38)	0 (0)	225 (62)
Tetracycline	58 (37)	14 (9)	85 (54)	65 (45)	14 (10)	66 (46)	145 (40)	35 (10)	181 (50)

Non-CP-CRE, Non carbapenemase-producer carbapenem-resistant Enterobacteriaceae; CP-CRE, Carbapenemase-producer carbapenem resistant Enterobacteriaceae; All CRE includes isolates tested and not tested for carbapenemase production; S, susceptible; I, intermediate; R, resistant, Pip-Tazo, piperacillin- tazobactam.

Table 3. Percent of carbapenem-resistant *Enterobacteriaceae,* in a large healthcare system in Miami-Dade County, 2012-2016.

	CRE	TOTAL tested	%
All *Enterobacteriaceae*	946	47,963	1.97
Klebsiella pneumoniae	487	9,922	4.91
Escherichia coli	151	23,151	0.65
Enterobacter sp	102	3,854	2.65

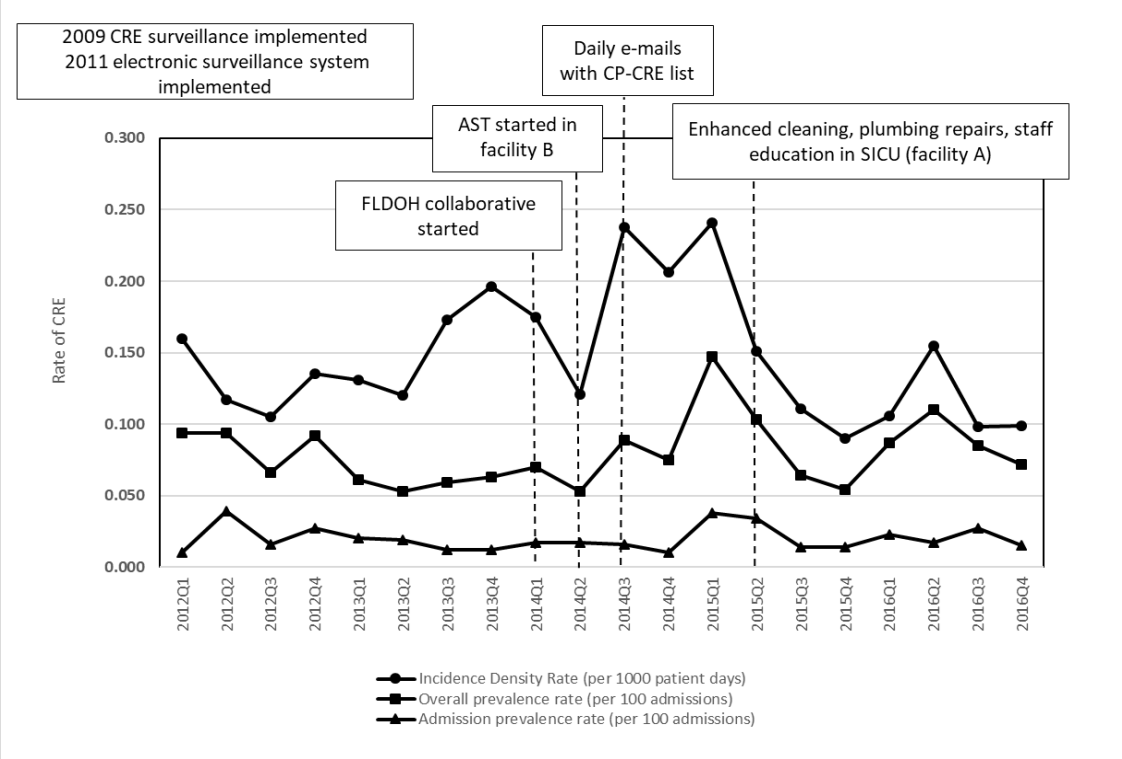
CRE carbapenem resistant *Enterobacteriaceae*

Table 4. Carbapenem resistant *Enterobacteriaceae* rates by facility of a large healthcare system in Miami-Dade County, 2012-2016.

	CRE overall prevalence rate (number of first CRE event per 100 admissions)	CRE admission prevalence (number of community-onset cases per 100 admissions)	CRE incidence density rate (number of hospital-onset per 10,000 patient days)
Facility A Major-teaching hospital	0.307	0.057	1.93
Facility B Community hospital	0.108	0.043	1.60
Facility C Community hospital	0.007	0.003	0.41
Facility D Major-teaching children hospital	0.035	0.008	0.56
All facilities	0.077	0.019	1.46

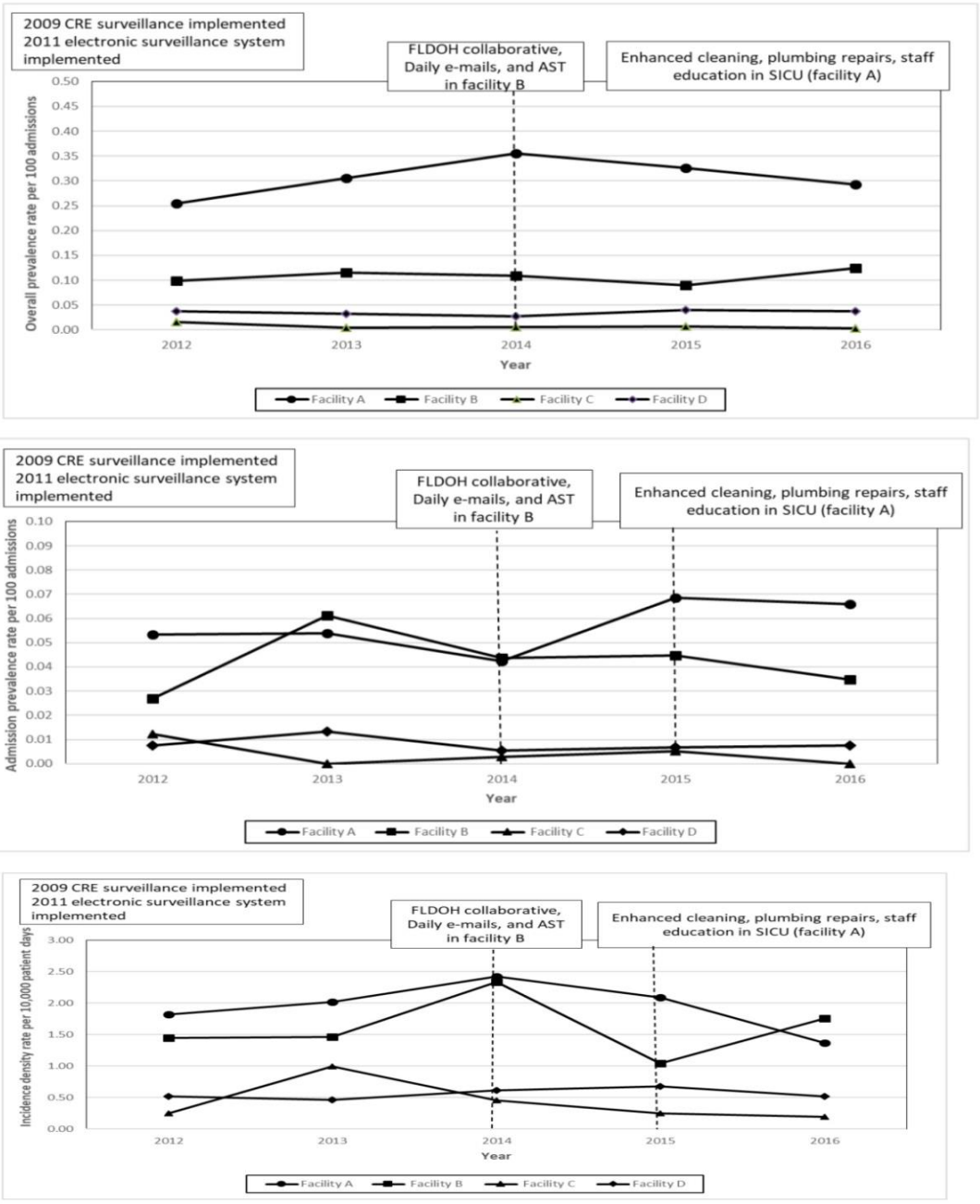
CRE, Carbapenem resistant *Enterobacteriaceae*; Overall prevalence = 1st CRE event /patient admissions x 100; Admission prevalence = number of community-onset events/patient admission x 100; Incidence density rate: number of hospital-onset cases/patient days x 10,000.

Figure 1. Prevalence and Incidence Rates by quarter for all facilities combined in a large healthcare system in Miami-Dade County, 2012-2016.



CRE carbapenem-resistant *Enterobacteriaceae*; FLDOH Florida Department of Health; AST active surveillance testing; CP-CRE carbapenemase producer *Enterobacteriaceae*; SICU surgical intensive care unit.

Figure 2. Carbapenem Resistant Enterobacteriaceae rates by facility in a large healthcare system in Miami-Dade County, 2012-2016



CRE, Carbapenem resistant Enterobacteriaceae; FLDOH, Florida Department of Health; AST active surveillance testing; SICU surgical intensive care unit; Overall prevalence rate = 1st CRE event /patient admissions x 100; admission prevalence rate = number of community onset events/patient admission x 100; Incidence density rate: number of hospital onset cases/patient days x 10,000.

MANUSCRIPT 2

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Risk factors for the development of infections associated with carbapenemase-producing *Enterobacteriaceae* among previously colonized patients: a retrospective cohort study

Abstract

Not all patients who acquire Carbapenemase-producing *Enterobacteriaceae* (CPE) develop infections by these organisms; many remain only colonized. Out of 54 CPE-colonized patients, 16 (30%) developed CPE infections. We identified indwelling urinary catheter exposure, exposure to intravenous colistin, and overseas transfer as variables associated with CPE infection development among colonized patients.

Background

Carbapenemase-producing *Enterobacteriaceae* (CPE) have spread globally and are considered urgent public health threats due to the increasing number of infections, limited options from treatment, and high mortality.[1,2] Carbapenemase production is an important mechanism of carbapenem resistance that contributes to the spreading of CPE since it is frequently plasmid-mediated and can be transferred among different species of *Enterobacteriaceae.*[1] Risk factors for CPE infection include residence in long-term-care facilities, use of medical devices, antibiotic exposures, and prior colonization with CPE.[1,3]

Not all CPE-colonized individuals develop CPE infection.[3,4] There are limited reports in the US describing factors associated with CPE infection after colonization; most studies are limited to rectal colonization while colonization of other body sites and associated infection has not been often studied.[4] We aimed to identify patient characteristics associated with CPE infections among patients previously colonized by the same organism.

Methods

This was a retrospective cohort study of CPE-colonized patients admitted to any of four hospitals in a large healthcare system (three adult and one pediatric, 2,500-beds) in Miami, Florida between 2012-2016. The study was approved by the Florida International University Institutional Review Board.

Rectal and tracheal aspirate (ventilated patients) surveillance cultures were collected on admission to adult intensive care units (ICU) and weekly thereafter until discharge/transfer out of the ICU. Surveillance cultures were processed in MacConkey plates following standard protocol (Supplementary material).

We included patients colonized at the time of first CPE identification; patients with first CPE isolated from a normally sterile source were excluded. Patients with first CPE isolated from a non-sterile source were evaluated for infection vs. colonization at the time of first identification; infections were defined using the National Healthcare Safety Network (NHSN) protocols[5] and review of infectious disease consultation and medical record. Colonized patients were followed through subsequent admissions for development of infection or censored. The probability of information bias by case

misclassification was reduced by reviewing every case by an infection disease physician and by infection preventionists during patient's admission and again retrospectively for the purposed of the study. Data were collected retrospectively from the electronic medical record and infection prevention database from the date CPE was first detected until the date of event of infection or censoring.

Baseline characteristics were compared using χ^2 or t-test. Kaplan-Meier was used to analyze the probability of developing CPE infections after colonization over time. Cox proportional hazards regression models were used to assess the association between predictors and the development of CPE infection. Statistical analysis was performed using SPSS 26 software (IBM, Armonk, NY).

Results

In total, 152 patients with CPE were identified during the study period; 98 were excluded, resulting in 54 (35%) included in the analysis (Supplementary Figure 1). Of the 54 colonized patients, 34 (80%) had *Klebsiella pneumoniae* (Table 1). Thirty-five isolates were tested by PCR; of those, 91% were positive for bla_{KPC}, and 9% for bla_{SME}. The most frequent source of colonization was rectal (41%), then urinary (35%), and respiratory (24%). Sixteen (30%) of the colonized patients developed CPE infection. Patient characteristics for both groups are presented in Table 1. Two (12%) patients had infections in three different body sites, eight (50%) had infections in two different body sites, and six (38%) had infection in one body site, yielding a total of 28 infections. The most frequent type of infections was bloodstream infections (39%), followed by pneumonia (32%), and urinary tract infections (18%) (Supplementary Table 1).

CPE-colonized patients were followed up for a mean of 304 days (IQR, 422). The mean time for infection development was 63 days (IQR=81; Range 0-7 months). Kaplan-Maier curve analysis (Supplementary Figure 2) showed that the probability of development CPE-related infections among colonized patients decreased over time, with a higher probability in the first three months after the identification of colonization.

After adjusting for significant variables in the multivariable Cox regression (Supplementary Table 2), CPE-colonized patients with indwelling urinary catheter (IUC) exposure (adjusted-Hazard Ratio [aHR] 4.4; *P*-value 0.034), exposure to colistin (aHR 3.17; *P*-value 0.037), or transferred from overseas (aHR 9.77; *P*-value 0.021) had a higher hazard of developing CPE infections (Table 2). Evaluation of those exposed to colistin showed that patients who developed CPE infection were exposed via intravenous route while those exposed to inhaled colistin did not; colistin was administered for treatment of extensively-drug-resistant (XDR) *Pseudomonas, Acinetobacter, or Stenotrophomonas*.

Discussion

We identified the use of indwelling urinary catheter (IUC) exposure to intravenous colistin, and transfer from overseas facilities as variables associated with the development of CPE infection. All infections occurred within 7 months of being identified as CPE colonized; the probability of developing CPE infections decreased over time possibly related to spontaneous colonization clearance.

Our findings are consistent with previous reports that identified CPE colonization as a risk factor for the development of CPE-related infections.[4,6] These studies focused on

rectal colonization. This study included other sources of colonization, finding that a higher percentage of those colonized in the respiratory tract developed infection although the difference was not statistically significant. Nevertheless, this finding highlights the importance of considering screening more than one anatomical site. Also, facilities should consider including in their CPE surveillance testing high-risk populations such as patients transferred from overseas.

In our cohort, 30% of the colonized patients developed CPE infections; this has implications for antibiotic selection. Colistin resurged as an option of treatment of XDR-*Pseudomonas, Acinetobacter, and Enterobacteriaceae* infections.[7] Until recently, there was no consensus about dosage and use of colistin for such infections or about antimicrobial susceptibility testing and breakpoints.[7] The possibility that resistance to colistin played a role in the development of the CPE infections among our cohort is unknown due to lack of reliable testing at the time of the study. *Pseudomonas* and *Acinetobacter* were tested against colistin by Etest; the reliability of this method has been largely questioned.[8] Recently, there has been an increasing number of reports related to colistin resistance; the mechanisms of colistin resistance are not yet fully understood.[9] Antimicrobial stewardship programs should tailor interventions to align with the recent recommendations for the use of colistin and recently available antimicrobials.

IUC are among the most commonly utilized devices in hospitals. [10] We found that exposure of these devices was associated with an increased probability of developing CPE infections in colonized patients; this finding concurs with previous reports.[3] Infection prevention interventions should aim to reduce the utilization of such devices

preventing catheter-associated urinary tract infections (CAUTI) as well as CPE infections.

This study has several limitations. First, the small sample size reduced the power to detect other possible associations. Second, active surveillance cultures were only collected from adult-ICU patients; among non-ICU patients, detection of colonization relied on the identification of CPE in clinical cultures, introducing selection bias and possibly information bias affecting the results and limiting generalizability of the study. Third, 91% of the isolates tested had bla_{KPC} as the resistance mechanism, facilities with higher prevalence of other carbapenemases might have different findings; further studies should explore this probability. Lastly, we introduced time-dependent bias by measuring exposure to devices and to antibiotics as categorical variables and possibly affecting the HR.

In conclusion, 30% of CPE-colonized patients developed infections associated with these organisms. We suggest reducing the use of IUC for patients colonized with CPE and implementing the use of alternative devices such as condom catheters or external female urinary catheters whenever possible. Furthermore, we suggest expanding CPE surveillance testing including other anatomical sources in addition to the rectum. Lastly, we recommend limiting the use of colistin among CPE-colonized patients to decrease the risk of infection as part of multidisciplinary interventions. Further studies should evaluate the effect of interventions such as selective decolonization, or fecal transplantation, to prevent the CPE infections among colonized patients.

Acknowledgments

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Table 1. Characteristics of patients colonized with Carbapenemase-producing *Enterobactericeae* (CPE) at a large health care system, 2012-2016

		No CPE Infection N= 38 (%)	CPE Infection N= 16 (%)	*P*-value
Gender	**Male**	27 (71)	8 (50)	0.139
	Female	11 (29)	8 (50)	
Age, mean (± SD)		58 (25)	63 (13)	0.467
Admission source when first identified as colonized with CPE	**Home**	21(55)	3 (19)	0.084
	Other hospital	7 (18)	7(44)	
	LTCF	7 (18)	4 (25)	
	Overseas	3 (8)	2 (12)	
Solid organ transplant		10 (26)	6 (37)	0.411
Immunocompromised		12 (32)	7 (44)	0.178
Steroids > 2 weeks		5 (13)	6 (37)	0.450
Surgery		25 (66)	13 (81)	0.256
Endoscopy		8 (21)	2 (12)	0.460
ICU admission		32 (84)	14 (87)	0.756
Charlson score, mean (± SD)		4.5 (2.5)	5.7 (2.9)	0.148
Comorbidities	DM with end-organ damage	6 (16)	3 (19)	0.496
	Congestive heart failure	1 (3)	3 (19)	*0.039
	Myocardial infarction	3 (8)	2 (12)	0.594
	Peripheral vascular disease	4 (10)	2 (12)	0.833
	Chronic kidney disease	12 (32)	5 (31)	0.981
	Cardiovascular disease	3 (8)	2 (12)	0.594
	Dementia	0 (0)	2 (12)	*0.026
	COPD	4 (10)	2 (12)	0.833
	Connective tissue disease	1 (3)	0 (0)	0.512
	Pepcid ulcer	1 (3)	0 (0)	0.512
	Moderate to severe liver disease	8 (21)	4 (25)	0.271
	Metastatic solid tumor	0 (0)	1 (6)	0.162
	AIDS	1 (3)	1 (6)	0.52
Central venous catheter		26 (68)	13 (81)	0.337
Indwelling urinary catheter (IUC)		19 (50)	13 (81)	*0.041
Ventilator		17 (45)	11 (69)	0.06
Organism	*Klebsiella pneumoniae*	23 (60)	11 (69)	0.754
	Enterobacter spp	8 (21)	1 (6)	

	Escherichia coli	2 (5)	1 (6)	
	Serratia marcescens	2 (5)	1 (6)	
	Citrobacter sp.	3 (8)	2(12)	
Colonization site	Rectal	16 (42)	6 (38)	0.724
	Urine	14 (37)	5 (31)	
	Respiratory	8 (21)	5 (31)	
Antibiotic exposure* **		35 (92)	15 (94)	0.833
Antibiotic days* **	< 4 days	6 (16)	1 (6)	0.446
	4-7 days	7 (18)	1 (6)	
	8-18 days	5 (13)	3 (19)	
	> 18 days	20 (53)	11 (69)	
Number of antibiotics* **	None	3 (8)	1 (6)	0.135
	1	3 (8)	1 (6)	
	2	1 (3)	1 (6)	
	3-4	15 (40)	1 (6)	
	>4	16 (42)	12 (75)	
Antibiotic class* **	Aminoglycosides	10 (26)	7 (44)	0.208
	1st -2nd gen cephalosporins	2 (5)	0 (0)	0.350
	3rd- 4th gen cephalosporins	25 (66)	11 (69)	0.833
	Carbapenem	18 (47)	11 (69)	0.150
	Daptomycin	1 (3)	3 (19)	*0.039
	Vancomycin	23 (60)	13 (81)	0.140
	Quinolones	12 (32)	16 (100)	*0.035
	Metronidazole	10 (26)	9 (56)	*0.035
	Sulfas	11 (29)	7 (44)	0.292
	Colistin	6 (16)	7 (44)	*0.028
	Penicillins	11 (29)	4 (25)	0.767
	Other	24 (63)	11 (69)	0.777
All cause death within 30-days of colonization detection.		8 (21)	6 (38)	0.208
All cause overall death after colonization detection.		13(34)	10 (62)	0.055

CPE= Carbapenemase-producing *Enterobacteriaceae*; SD = standard deviation; LTCF= long-term-care facility; ICU =intensive care unit; DM= diabetes mellitus; COPD= Chronic obstructive pulmonary disease; AIDS = Acquired immunodeficiency syndrome; IUC= Indwelling urinary catheter

*** *P*-value < 0.05**

*****Antibiotic exposures were measured since first identified as colonized until date of event for infections, censoring date, or end of study period whichever occurred first.**

Table 2. Reduced model for CPE infection among colonized patients at a South Florida Healthcare System 2012-2016.

		aHR	95%CI	*P-v*alue
Foley		4.4	1.11-17.38	*0.034
Colistin		3.17	1.072-9.37	*0.037
Admission source	Home	ref		0.105
	Another hospital	3.54	0.87-14.42	0.078
	LTCF	4.32	0.91-20.42	0.065
	Overseas	9.77	1.40-67.93	*0.021

*** P-value ≤ 0.05**

CPE= carbapenemase producing *Enterobacteriaceae; a*HR = Adjusted Hazard ratio; CI = confidence interval; LTCF = Long-term-care facility.

Supplementary materials (Available only online)

Carbapenemase-producing Enterobacteriaceae cultures process description.

The surveillance samples were cultured on MacConkey agar plates with 10 µg meropenem and ertapenem disks. Organism identification and full susceptibility testing from surveillance and clinical isolates were performed using the Vitek2® system. Carbapenemase production was tested phenotypically with the Modified Hodge Test until 2014 and using CarbaNP Test starting in 2015. Isolates were frozen for epidemiological reasons. For the purpose of this study, viable isolates were tested by PCR in 2019 to detect bla_{KPC}, bla_{NDM}, and bla_{OXA-48}; *Serratia marcescens* isolates were also tested for bla_{SME}.

Supplementary Table 1. CPE-infection types based on initial colonization source among patients admitted to large healthcare system in Miami FL. 2012-2016.

	Initial Colonization Source			
	Rectal N=11 (%)	**Respiratory N=8 (%)**	**Urinary tract N=9 (%)**	**Total Infections N=28 (%)**
BSI	3 (27)	3 (38)	4 (44)	10 (36)
UTI	2 (18)	1 (12)	2 (22)	5 (18)
PNU	4 (36)	4 (50)	0 (0)	8 (26)
SSI	1 (9)	0 (0)	0 (0)	1(4)
IAB	1 (9)	0 (0)	3 (33)	4 (14)

BSI= blood stream infections; UTI= urinary tract infections; PNU= pneumonia; SSI = surgical site infection; IAB = Intrabdominal infection

Supplementary Table 2. Cox proportional hazards ratios by predictors for CPE infection among colonized patients at a large health care system in Miami, Florida 2012-2016

		Bivariable regression			Multivariable regression Full Model		
		HR	**95% CI**	***P*-value**	**aHR**	**95% CI**	***P*-value**
Gender	Female	0.67	0.25-1.78	0.418			
Age, mean (± SD)		1.01	0.99-1.04	0.252			
Admission source	Home	ref		0.710	ref		0.24
	Other hospital	5.21	1.33-20.35	**0.018	2.12	0.39-11.47	0.385
	LTCF	3.95	0.87-17.88	*0.074	5.91	1.28-27.37	**0.039
	Overseas	8.78	1.35-57.20	**0.023	14.85	1.43-53.80	**0.024
Solid organ transplant		1.12	0.41-3.12	0.821			
Immunocompromised		1.43	0.53-3.82	0.480			
Steroids > 2 weeks		2.48	0.90-6.83	*0.079	3.04	0.79-11.70	0.106
Surgery		1.41	0.40-4.97	0.589			
Endoscopy		0.58	0.13-2.58	0.478			
ICU admission		0.61	0.14-2.70	0.516			
Charlson score		1.13	0.95-1.35	0.167			
Devices	CVC	1.68	0.48-5.94	0.417			
	IUC	3.90	1.10-13.8	**0.035	5.94	1.28-27.37	**0.023
	Ventilator	2.98	0.96-9.27	*0.059	1.19	0.28-5.09	0.814
Organism	*Klebsiella pneumoniae*	ref		0.936			
	Enterobacter sp	0.46	0.06-3.61	0.464			
	Escherichia coli	1.05	0.13-8.15	0.963			
	Serratia marcescens	1.3	0.29-5.89	0.733			
	Citrobacter sp.	1.35	0.17-10.53	0.775			
Colonization site	Rectal	ref		0.678			
	Urine	1.08	0.33-3.54	0.902			

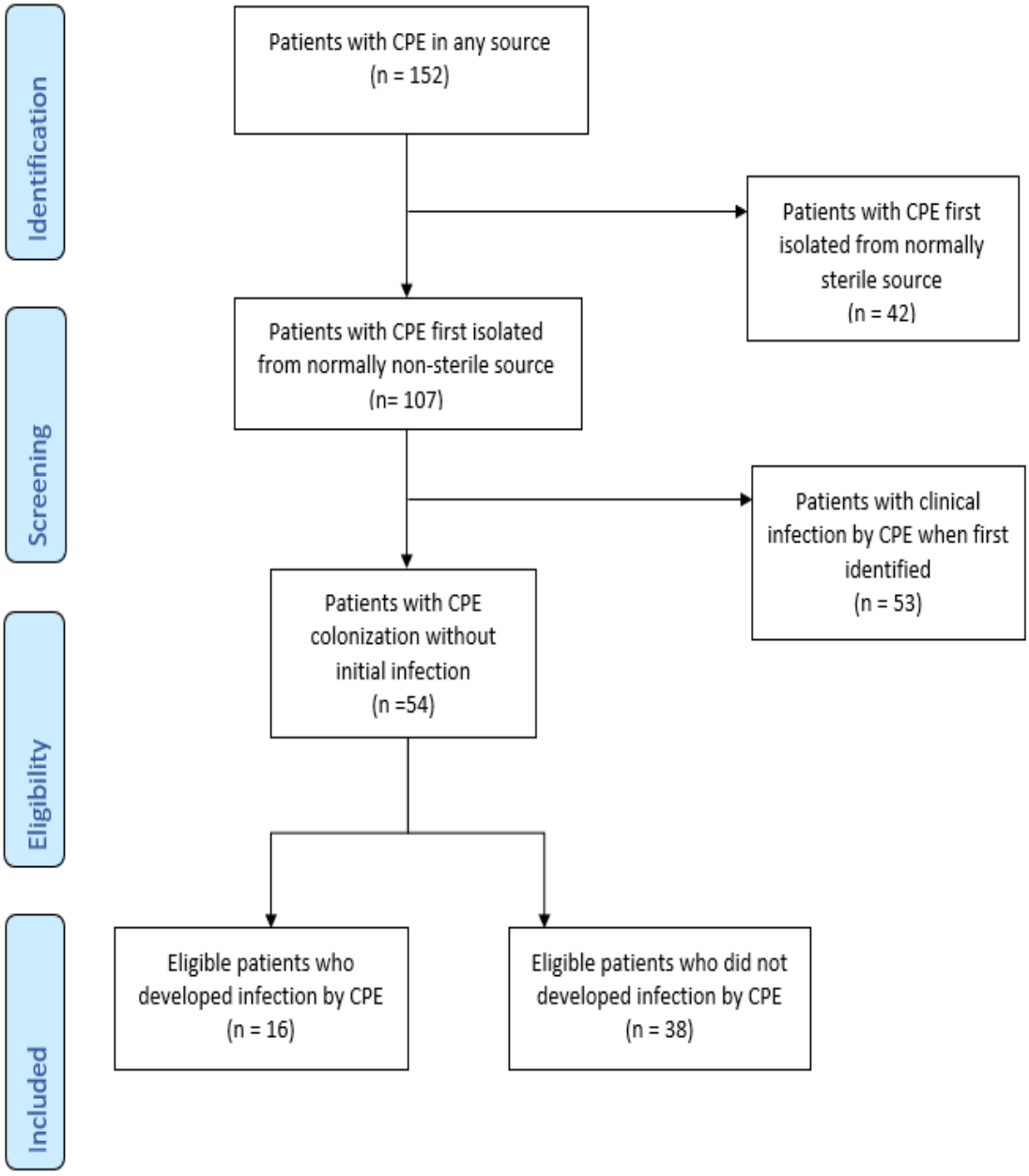
	Respiratory	1.66	0.50-5.44	0.405			
Antibiotic exposure		1.54	0.20-11.65	0.678			
Antibiotic days	< 4 days	ref		0.419			
	4-7 days	1.42	0.09-22.77	0.804			
	8-18 days	5.45	0.56-53.18	0.145			
	> 18 days	2.63	0.34-20.43	0.355			
Number of antibiotics	None	ref		0.340			
	1	1.42	0.089-22.86	0.802			
	2	3.98	0.24-64.81	0.332			
	3-4	0.31	0.019-4.93	0.405			
	>4	2.17	0.28-16.70	0.458			
Antibiotic class	Aminoglycosides	1.58	0.59-4.25	0.364			
	3rd-4th gen ceph	1.12	0.39-3.22	0.839			
	Carbapenem	2.21	0.76-6.39	0.144			
	Vancomycin	3.00	0.85-10.60	*0.089	1.32	0.25-6.91	0.744
	Quinolones	2.23	0.81-6.12	0.122			
	Metronidazole	3.00	1.10-8.17	**0.031	1.04	0.25-4.39	0.955
	Sulfas	1.37	0.51-3.69	0.529			
	Colistin	2.76	1.02-7.42	**0.045	3.13	0.85-11.50	0.086
	Penicillins	0.75	0.24-2.34	0.622			
	Other	1.19	0.41-3.42	0.752			

*** p-value <0.1**

**** p-value <0.05**

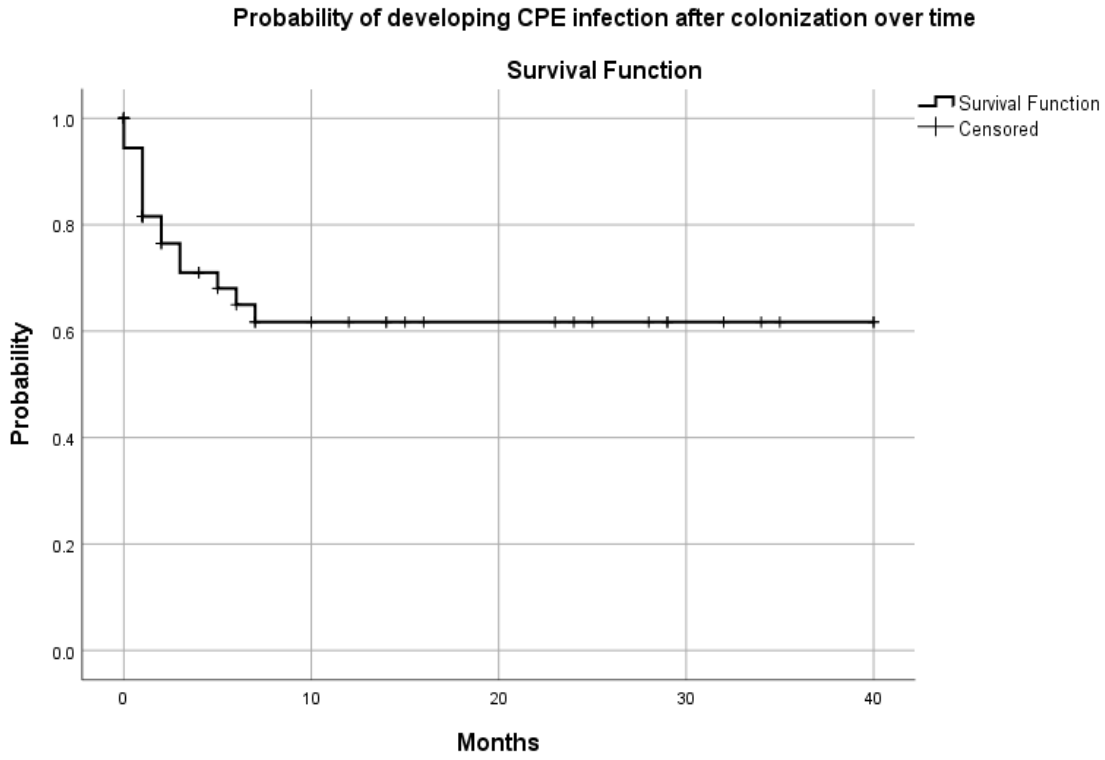
CPE = Carbapenemase producing *Enterobacteriaceae;* HR= Hazard Ratio; aHR= Adjusted Hazard Ratio; CI = confidence interval; SD= standard deviation; ref = reference ; LTCF = long-term-care facility; ICU= Internsive care unit; CVC= Central Venous Catheter; IUC= Indwelling urinary catheter; 3rd-4th gen ceph= 3rd-th generation cephalosporins.

Supplementary Figure 1. Patient selection algorithm, patients colonized with CPE in la large healthcare system in Miami, FL 2012–2016.



CPE= carbapenemase-producing *Enterobacteriaceae*

Supplementary Figure 2. Kaplan-Meier curve for CPE-colonized patients hazard of developing infections by CPE over time.



CPE = Carbapenemase-producing *Enterobacteriaceae*.

MANUSCRIPT 3

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Duration of Carbapenemase-producing Enterobacteriaceae Carriage among Hospitalized Patients in Miami, FL: a Retrospective Cohort Study.

Abstract

Background

Current recommendations by the Centers for Disease Control and Prevention (CDC) suggest placing patients with carbapenem-producing Enterobacteriaceae (CPE) in contact precautions (CP), but there is no consensus on the appropriate duration of precautions. We aimed to evaluate predictors for prolonged CPE carriage and median clearance time.

Methods

Hospitalized patients with first isolated CPE identified from 2012 to 2016 were followed for clearance of CPE using at least two rectal or tracheal aspirate surveillance cultures and clinical cultures. Predictors associated with prolonged CPE carriage were assessed using Cox proportional hazards.

Results

Out of 75 eligible patients, 25 (33%) cleared their CPE-carrier status; the median time to clearance was 80 days (Range, 16–457). Patients who were immunocompromised, had mechanical ventilation exposure, or exposure to carbapenems had 66%, 66%, and 86 % (HR, 0.34, 0.34, and 0.14, respectively [*P*-value <0.05]) lower probability of clearing their CPE carrier status compared to those immunocompetent or without such exposures.

Patients with CPE isolated from more than one anatomical body site had a 5.3 times higher probability of clearing their CPE-carrier status *(P*-value <0.001).

Conclusion

Patients immunocompromised, with mechanical ventilation exposure, or exposure to carbapenems had higher risk for prolonged CPE carriage. Infection prevention programs should consider these predictors as part of their assessment of discontinuing contact precautions among CPE carriers to prevent horizontal transmission and outbreaks within healthcare facilities.

Background

Since the first reports in the early 1990s, Carbapenem-resistant Enterobacteriaceae (CRE) have spread across the world [1-3]. CRE are a public health threat globally due to their rapid spread, and limited treatment options. CRE can be resistant to carbapenems by different mechanisms including production of carbapenemases [1,4-6]. Carbapenemase-producing Enterobacteriaceae (CPE) synthesize β-lactamases that hydrilyze carbapenems, rendering the treatment with this class of antibiotics ineffective.

The Centers for Disease Control and Prevention (CDC) recommendations for healthcare facilities to prevent and control the transmission of CPE include placing CPE patients on contact precautions (CP), as well as cohorting patient and staff [7]. These recommendations do not provide guidance about when to discontinue CP. The few studies that have assessed the duration of carriage of CPE have been conducted mainly outside the US [8-15]; thus, there is limited research on this topic in US healthcare settings. In 2018, the Society for Healthcare Epidemiology of America (SHEA) published expert

guidance regarding the duration of CP for acute-care facilities in the case of CPE [13]. In their systematic review, the authors found wide variability in the median time for CPE clearance. Most of the studies included in the review were from Israel, China, or Europe. They also reported that only 32% of the facilities in the US had policies allowing the discontinuation of CP for CRE. Of those with policies, 28% reported using screening tests for discontinuing CP, and 38% reported using a 'greater than one year since the last positive test' rule to discontinue CP. The expert guidance recommends maintaining CP indefinitely for extensively drug-resistant *Enterobacteriaceae* such as CPE [13]. We therefore aimed to evaluate the duration of CPE carriage and factors associated with its prolonged carriage among patients admitted to the hospitals of the largest healthcare system in Miami, FL.

Methods

This was a retrospective cohort study among patients admitted between January 2012 and December 2016 to any of the four hospitals of the health system. The system comprises two community hospitals and two major referral tertiary-care teaching centers, one adult and one pediatric. The system has over 2,000-licensed hospital beds and includes several medical specialties including trauma, burns, one of the largest solid organ transplant centers in the US, an 80-bed inpatient rehabilitation facility, two long-term care facilities, and numerous outpatient clinics. As previously described [16], all patients admitted to adult ICUs were screened for CPE colonization. Rectal and tracheal aspirate (ventilated patients) cultures were collected upon admission to the ICU and weekly thereafter until discharge or transfer out of the ICU. The surveillance samples were cultured on MacConkey agar plates with 10 µg meropenem and ertapenem disks

after enrichment in Trypticase Soy Broth and meropenem disk. Organism identification and susceptibility testing from surveillance and clinical isolates were performed using the Vitek2® system. Carbapenemase production was tested with the Modified Hodge Test until 2014 and using CarbaNP Test beginning in 2015. Isolates were routinely frozen for later epidemiologic analysis. Viable isolates were sub-cultured and tested by PCR in 2019 to detect *bla*$_{KPC}$, *bla*$_{NDM}$, and *bla*$_{OXA-48}$; *Serratia marcescens* isolates were also tested for *bla*$_{SME}$ as previously described [5,17].

We included patients that had their first CPE detected in either surveillance or clinical cultures and who also had two or more subsequent surveillance cultures collected during admission to any of the facilities during the study period. Patients with their first CPE isolated prior to the study period were excluded. We followed eligible patients from the time they were first determined as CPE carriers until they were considered cleared/censored, including subsequent admissions to any of the system facilities. Patients with prolonged CPE carriage were censored when last seen in any of the system facilities or at the end of the study period. A patient was considered CPE cleared when he/she had two or more negative surveillance cultures from the initial source (rectal or respiratory), and other CPE were not isolated from any other clinical cultures. If the first CPE was identified in clinical culture, at least one negative culture had to be collected from the same site. A patient was considered recurrent if after meeting clearance criteria, a CPE was isolated from any culture. Patients were considered immunocompromised based on CDC definition [18] which included: neutropenic, those with leukemia, lymphoma or who are HIV positive with CD4 count <200 cells/µL, those who have undergone splenectomy, history of solid organ or hematopoietic stem cell transplant, those on

cytotoxic chemotherapy, on enterally or parenterally administered steroids (excluding inhaled and topical steroids) daily for more than two weeks.

Data were collected retrospectively using the electronic medical record (Cerner Corp©) and the Infection Prevention and Control Surveillance System platform (Vigilanz Corp©). Antibiotic and device exposures were collected as categorical (yes/no) variables at any time from first CPE isolation to clearance, censoring, or end of the study. The study was approved by the Florida International University Institutional Review Board and the health system's Office of Research.

Baseline characteristics of the groups were compared based on clearance status using $\chi 2$ and Fisher exact tests for proportions and Student t-tests for continuous variables. Median carriage time was determined using the Kaplan-Meier curve. Factors associated with a prolonged carriage were analyzed using Cox proportional survival analysis [19]. The assumption of proportionality was evaluated using survival curves for each variable, and variables that violated the assumption were excluded [20]. Bivariable and multivariable Cox proportional hazards regression models were used to assess the association between predictors and CPE clearance. We obtained hazard ratios and 95% confidence intervals. Interactions between different antibiotic combinations frequently used for CPE treatment at the time of the study were also evaluated as predictors for CPE clearance. Multivariable Cox regression analyses included variables with *P*-value <0.1 in bivariable analysis, and the backward stepwise procedure was used to select the best model. The variables included in the multivariable analysis were assessed for multicollinearity. Statistical analysis was performed using SPSS version 27 software (IBM, Armonk, NY).

Results

During the study period, there were 152 unique patients with their first CPE identified through surveillance or clinical cultures across the four hospitals; of those, 75 (49.3%) patients met the study inclusion definition after 77 (50.6%) were excluded due to the lack of more follow up surveillance cultures. Patients included in the final analysis were followed for a median time of 83 days (IQR, 36–241 days) and a maximum of 1,754 days (58 months). Most patients had the first CPE isolated from urine (39%), followed by respiratory tract (35%), and rectal (16%) (Table 1). The most frequent CPE identified was *Klebsiella* spp. (61%), followed by *Enterobacter* spp. (15%). For carbapenemases produced by CPE isolates, *Klebsiella pneumoniae* carbapenemase (KPC) accounted for 69% while New Delhi Metallo-β-lactamase (NDM) accounted for 4%. Fifty (67%) patients had CPE isolated from more than one body site with a maximum of four sites. The median time from first detection to last CPE positive culture was 24 days (Range, 0–1,252). Eleven (15%) patients only had one CPE positive culture. Twenty-five (33%) patients met the criteria for CPE clearance; the overall median time for clearance was 80 days (Range, 16–457). Of the 25 cleared patients, 15 (60%) cleared within 3 months, 19 (76%) within 6 months, 22 (88%) within one year, and all 25 by 15 months. Nineteen (76%) of the patients were cleared within the same index admission with a median length-of-stay of 69 days (Range 54-428 days). Recurrence was detected in 8 (32%) of the cleared patients; the median time to recurrence was 40 days (Range, 10-671 days). Baseline characteristics of groups based on clearance are presented in Table 1. There was no statistically significant difference in mortality rates between the two groups.

Bivariable Cox proportional regression showed crude hazard ratios with *P*-value < 0.1 for females, immunocompromised patients, exposure to mechanical ventilator, exposure to carbapenems, and CPE isolated from more than 1 body site (Table 2). Analysis of the effect of interactions between different classes of antibiotics and time to clearance did not show any statistically significant associations. After adjusting for all variables in the Cox proportional multivariable analysis model, immunocompromised patients had a 66% (*P*-value, 0.014) lower probability of clearing CPE compared to immunocompetent patients. Patients who experienced mechanical ventilator also had a 66% lower probability of clearance compared to those without such exposure (*P*-value, 0.016). Patients with exposure to carbapenems had a 86% lower probability of clearance compared to those without exposure to carbapenems(*P*-value, 0.010). Interestingly, patients with CPE isolated from more than one anatomical site had a 5.3 times higher probability of CPE clearance than those who had CPE isolated from only 1 body site (*P*-value <0.001) (Table 3). A deeper look into the cleared patients who had CPE isolated from more than one anatomical site revealed that 12 (86%) had CPE-related infections and only 2 (14%) were deemed as colonized. Figure 1 shows the probabilities over time of CPE clearance based on exposure to mechanical ventilator, exposure to carbapenems, and being immunocompromised, or having CPE isolate from more than one body site.

Discussion

This study evaluated the duration of CPE carriage and determinants for prolonged carriage among hospitalized patients. Patients had positive CPE cultures identified up to 42 months after the initial positive culture; only 33% of the patients met the criteria for clearance within 15 months. We found that patients who were immunocompromised,

exposed to mechanical ventilation or treated with carbapenems had a lower probability of clearance of CPE. Remarkably, those patients that had CPE isolated from more than one anatomical site had over 5 times the probability of achieving clearance compared to those that only had CPE isolated from one body site; this finding perhaps represents instances of effective therapy and source control of CPE-related infections because most of those patients had systemic infections. Our institution does not utilize decolonization therapy strategies for CPE carriers. Furthermore, during the study period, β-lactamase inhibitor combinations were not widely available. Ceftazidime/avibactam (CZA) was approved in mid-2015 for the treatment of complicated urinary tract infection or intraabdominal infections [21]. During the study period, treatment for CPE infections was tailored on a case-by-case basis; CZA was used on a few occasions, mostly under compassionate use near the end of the study. On the contrary, those patients who had CPE isolated only from one body site were deemed to be colonized and thus did not receive therapy targeting CPE.

Unfortunately, current CDC recommendations for control of CPE do not include guidance on how long a patient, either colonized or infected, should remain on CP to prevent horizontal transmission in acute care facilities,[7] leaving it up to each facility to determine how long to maintain CP for these patients during index admission and subsequent readmissions. Placing patients on CP indefinitely with dedicated staff places an extra burden on the facility. European recommendations establish a case-by-case approach based on risk factors in consultation with the infection prevention team for discontinuation of CP [22]. Several studies have assessed the duration of CPE colonization; most of these studies were from outside the US and relied only on the findings from

rectal surveillance cultures [14,15,23,24]. Moreover, previous studies have shown that screening from more than one anatomical site increases the chances of detecting CPE [25]. In our cohort, we found that 21 of the cases never demonstrated positive results in rectal surveillance cultures but did show positive results from respiratory specimens. Criteria for discontinuation of CP should include CPE negative cultures concordant with the anatomical site from where CPE was previously isolated and more than one negative screening culture. Furthermore, our study identified findings similar to other studies with a median time to clearance greater that 60 days and findings of CPE long-term carriage for longer than three years [26]. This finding is important to consider when using the case-by-case approach recommended in European guidelines, particularly in subsequent readmissions. Moreover, it is not possible to provide a blanket, empiric recommendation for CP discontinuation without testing.

Our study found that exposure to carbapenems was associated with prolonged CPE carriage; this highlights the importance of antimicrobial stewardship interventions to prevent unnecessary exposures to carbapenems that might select resistant strains that facilitate prolonged CPE carriage and increase the risk of infections by these organisms. We recently reported the development of algorithms for testing of carbapenem resistant Gram-negative rods; before implementation of these algorithms, the identification of CPE took a median time of 5 days, delaying timely treatment and implementation of proper isolation precautions [27]. Further research should aim to evaluate the effect of such interventions to shorten time to appropriate therapy and the effect in the time to CPE-carriage clearance.

Furthermore, previous studies suggested differences in the duration of CPE carriage based on the type of carbapenemase produced with KPC-producing isolates showing a longer duration of colonization compared to NDM-producing isolates[24]. In this study, we were unable to find similar results since most of the CPE tested were KPC-producing with limited representation of other carbapenemases; further studies are needed to assess possible differences in duration of CPE carriage based on the type of carbapenemase produced.

Our study had several limitations. First, we had a small sample size that might limit the power to detect the effect that certain predictors might have over the time for clearance of CPE carrier status. Second, in our institution, only patients admitted into an adult ICU had surveillance cultures collected routinely; this introduced selection bias to the study limiting the generalizability of our findings by excluding the patient population that has never been admitted to an ICU. Future studies should assess factors associated with prolonged CPE carriage among non-ICU patients and those in the community without hospital exposure. Furthermore, 50% of eligible patients were excluded due to limited follow up surveillance cultures which could have biased our results. Additionally, at the time of the study, the laboratory procedure test used for the surveillance cultures was not very sensitive, introducing potential measurement bias. Using more than one surveillance culture and requiring agreement with the initial anatomical source of CPE isolation likely compensated for the lower sensitivity of the procedure.

Conclusion

In conclusion, infection prevention and antimicrobial stewardship practices should consider risk factors for prolonged CPE carriage to limit transmission and select

suitable treatment options to optimize success at eradication, limit transmission, and safely discontinue isolation precautions. Further studies are needed to identify risk factors for long-term CPE carriage in different populations and to clarify possible differences for duration of CPE carriage related to microorganism specific species and type of carbapenemase.

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Table 1. Characteristics of CPE carriers at a large health care system 2012–2016				
		CPE Carrier Not Cleared N= 50 (%)	**CPE Carrier Cleared N= 25 (%)**	**Chi square p-value**
Sex, Female		24 (48)	17 (68)	0.101
Age, mean (± SD)		64 (14.3)	54.1 (18.8)	0.014*
Admission source	Home	23 (46)	9 (36)	0.845
	Other hospital	12 (24)	8 (32)	
	LTCF	11 (22)	6 (24)	
	Overseas	4 (8)	2 (8)	
Solid organ transplant		11 (22)	8 (32)	0.348
Immunocompromised		19 (38)	14 (56)	0.139
Steroids >2 weeks		9 (18)	7 (28)	0.319
Surgery		30 (60)	17 (68)	0.500
Endoscopy		14 (29)	10 (40)	0.350
ICU admission		40 (80)	22 (88)	0.388
Charlson score , mean (± SD)		5.34 (2.8)	5.12 (2.6)	0.745*
Comorbidities	Diabetes mellitus with end organ damage	4 (8)	2 (8)	0.352
	Congestive heart failure	7 (14)	1 (4)	0.186
	Myocardial infarction	6 (12)	2 (8)	0.597
	Peripheral vascular disease	5 (10)	1 (4)	0.367
	Chronic kidney disease	15 (30)	7 (28)	0.858
	Cardiovascular disease	8 (16)	2 (8)	0.337
	Chronic obstructive pulmonary disease	7 (14)	1 (4)	0.186
	Connective tissue disease	2 (4)	0(0)	0.311
	Moderate to severe liver disease	2 (4)	7 (28)	0.005
	Localized solid tumor	3 (6)	2 (8)	0.423
	Metastatic solid tumor	1 (2)	2 (8)	
	Human immunodeficiency virus	3 (6)	2 (8)	0.743
Central venous catheter exposure		30 (60)	18 (72)	0.307
Indwelling urinary catheter exposure		32 (64)	14 (56)	0.502
Ventilator exposure		22 (44)	14 (56)	0.327
Organism	*Klebsiella* spp.	27 (54)	19 (76)	0.179
	Enterobacter spp.	10 (20)	1 (4)	
	Escherichia coli	4 (8)	2 (8)	
	Serratia marcescens	4 (8)	0(0)	
	Citrobacter spp.	5 (10)	3 (12)	
Carbapenemase	bla_{KPC}	34 (68)	18 (72)	0.792

gene	*bla*$_{NDM}$	2 (4)	1 (4)	
	bla$_{SME}$	2 (4)	0(0)	
	Unknown/not tested	12 (24)	6 (24)	
Initial carriage source	Rectal	5 (10)	7 (28)	0.163
	Blood	0 (0)	1 (4)	
	Urine	23 (46)	6 (24)	
	Respiratory	18 (36)	8 (32)	
	Wound/drainage	3 (6)	2 (8)	
	Other	1 (2)	1 (4)	
CPE isolated from >1 body site		36 (72)	14 (56)	0.166
Antibiotic exposure		48 (96)	25 (100)	0.311
Antibiotic days	< 4 days	3 (6)	1 (4)	0.280
	4-7 days	5 (10)	0(0)	
	8-18 days	7 (14)	2 (8)	
	> 18 days	35 (70)	22 (88)	
Number of antibiotics	None	2 (4)	0(0)	0.580
	1	3 (6)	0(0)	
	2	2 (4)	1 (4)	
	3-4	9 (18)	4 (16)	
	>4	34 (68)	20 (80)	
Antibiotic class	Aminoglycosides	17 (34)	13 (52)	0.134
	1st -2nd gen cephalosporins	2 (4)	3 (12)	0.190
	3rd- 4th gen cephalosporins	34 (68)	19 (76)	0.473
	Carbapenems	32 (64)	23 (92)	**0.010
	Daptomycin	7 (14)	3 (12)	0.810
	Vancomycin	41 (82)	23 (92)	0.249
	Macrolides	5 (10)	4 (16)	0.451
	Quinolones	25 (50)	16 (64)	0.251
	Metronidazole	21 (42)	11 (44)	0.869
	Sulfas	17 (34)	13 (52)	0.134
	Colistin	21 (42)	12 (48)	0.622
	Penicillins	24 (48)	14 (56)	0.514
	Ceftazidime/avibactam	3 (6)	1 (4)	0.716
	Other	28 (56)	13 (52)	0.743
Mortality at 30 days		8 (16)	1(4)	0.132
Overall mortality		19 (38)	10 (40)	0.867

CPE= carbapenemase-producing *Enterobacteriaceae*; SD = standard deviation; LTCF= long-term-care facility; ICU =intensive care unit; COPD= Chronic obstructive pulmonary disease; AIDS = Acquired immunodeficiency syndrome.
***t*-test *P*-value**

Table 2. Predictors for clearance of CPE carriage at a large health care system in South Florida, 2012–2016

		Univariable Hazard ratio	95% CI	p-value	Multivariable Hazard ratio	95% CI	p-value
Gender	Female	0.70	0.46-1.06	*0.093	0.71	0.28-1.70	0.416
Age, mean		0.99	0.96-1.01	0.258			
Admission source	Home	Ref		0.668			
	Other hospital	0.67	0.35-1.31	0.244			
	LTCF	0.86	0.43-1.70	0.670			
	Overseas	1.11	0.53-2.33	0.776			
Solid organ transplant		1.49	0.64-3.48	0.354			
Immunocompromised		0.65	0.43-0.97	**0.036	0.38	0.15-0.93	**0.034
Steroids >2 weeks		0.79	0.51-1.23	0.298			
Surgery		0.96	0.63-1.46	0.836			
Endoscopy		1.19	0.53-2.67	0.667			
ICU admission		0.65	0.35-1.18	0.158			
Charlson score		1.15	0.95-1.39	0.145			
Comorbidities	Diabetes mellitus with end organ damage	0.641	0.29-1.39	0.258			
	Congestive heart failure	1.373	0.50-3.76	0.538			
	Myocardial infarction	1.43	0.69-2.96	0.329			
	Peripheral vascular disease	1.64	0.60-4.48	0.330			
	Chronic kidney disease	0.93	0.59-1.48	0.759			
	Cardiovascular disease	1.44	0.70-2.97	0.322			

	COPD	1.49	0.55-4.01	0.438			
	Chronic lung disease	1.30	0.48-3.53	0.611			
	Connective tissue disease	0.04	0.00-115.7	0.440			
	Liver disease	0.72	0.46-1.11	0.137			
	HIV	1.10	0.26-4.69	0.895			
Devices	Central Venous catheter	0.73	0.47-1.13	0.16			
	Indwelling urinary catheter	1.11	0.75-1.65	0.611			
	Ventilator	0.70	0.47-1.04	*0.075	0.38	0.16-0.92	**0.031
Organism	*Klebsiella* spp.	ref		0.520			
	Enterobacter spp.	0.21	0.03-1.56	0.127			
	Escherichia coli	0.59	0.14-2.54	0.476			
	Citrobacter spp.	0.56	0.17-1.93	0.362			
	Serratia marcescens	0.00	0.00	0.980			
Carbapenemase gene	bla_{KPC}	ref		0.956			
	bla_{NDM}	1.26	0.50-3.19	0.624			
	bla_{SME}	0.89	0.11-7.46	0.914			
	Unknown/not tested	0.00	0.00	0.982			
CPE isolated from >1 body site		2.05	0.93-4.52	*0.075	5.01	2.03-12.36	**<0.001
Antibiotic exposure	Aminoglycosides	0.84	0.57-1.25	0.393			
	1st -2nd gen cephalosporins	0.93	0.50-1.70	0.802			
	3rd- 4th gen cephalosporins	1.06	0.67-1.68	0.810			
	Carbapenem	0.50	0.24-1.03	*0.062	0.14	0.03-0.63	**0.011
	Daptomycin	1.03	0.56-1.88	0.928			

	Vancomycin	0.77	0.37-1.59	0.480
	Macrolides	1.14	0.67-1.96	0.626
	Quinolones	0.96	0.63-1.44	0.826
	Metronidazole	1.15	0.76-1.72	0.509
	Sulfas	0.87	0.54-1.28	0.477
	Colistin	0.98	0.66-1.46	0.930
	Penicillins	1.07	0.72-1.59	0.736
	Other	1.11	0.75-1.64	0.612
	Ceftazidime/avibactam (CZA)	1.34	0.49-3.64	0.570

*** p-value <0.1**

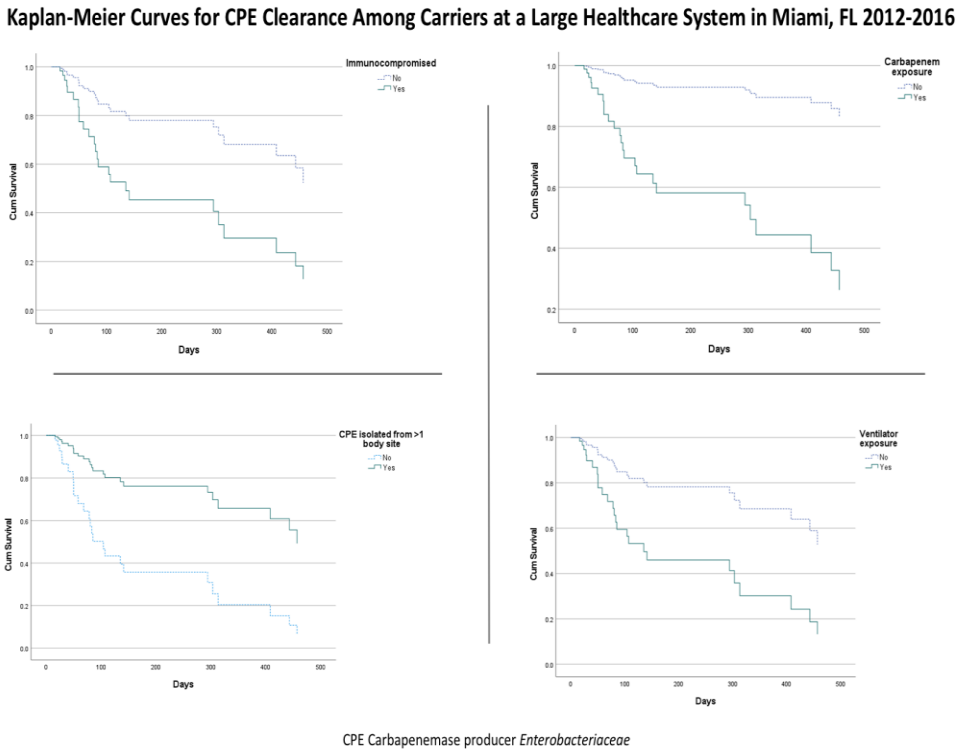
**** p-value <0.05**

CPE = Carbapenemase-producing *Enterobacteriaceae;* CI = confidence interval; SD= standard deviation; LTCF = long-term-care facility; ICU= Intensive care unit.

Table 3. Predictors for Clearance of CPE Carrier status at a Healthcare System in Miami, FL 2012–2016—Reduced Model.

	aHR	95%CI	*P*-value
Ventilator	0.34	0.14-0.82	*0.016
Immunocompromised	0.34	0.14-0.80	*0.014
Carbapenems exposure	0.14	0.03-0.62	*0.010
CPE isolated from >1 body site	5.27	2.12-13.07	*<0.001
*** P-value ≤0.05**			
CPE= carbapenemase-producing *Enterobacteriaceae; a*HR = Adjusted Hazard ratio; CI = confidence interval			

Figure 1.



CONCLUSIONS

The epidemiology of carbapenem-resistant *Enterobacteriaceae* (CRE) among a cohort of patients admitted to an acute-care setting in Miami, FL is similar to that described in other highly populated areas in the US. *Klebsiella pneumoniae* was the most frequent species of CRE identified. Similarly, KPC was the most frequent carbapenemase detected. CRE accounted for 2% of all the *Enterobactericeae* tested during the study period; this percentage is similar to the current estimate for Florida (2.1%) and lower than the one for the US (2.7%).

The use of an internal CRE registry integrated with the EMR contributed to the control of increasing CRE rates by rapidly identifying readmissions and allowing immediate initiation of proper isolation, infection prevention interventions, and appropriate antimicrobial stewardship management. Similar registries implemented at a regional or state level would have a greater impact on controlling the spread of CRE across the US by allowing automatic electronic identification of known CRE carriers transferred or admitted to different healthcare system networks. This would also allow public health authorities to allocate adequate resources for their HAI prevention programs and target regions with higher numbers of CRE reported to the registry.

In the same way, active surveillance testing is a key component in controlling the spread of CRE/CPE by increasing the early detection of carriers and facilitating the timely implementation of infection prevention strategies. Active surveillance testing should include populations at risk for CRE carriage. The ICU population has been widely recognized as being at higher risk for the acquisition of these organisms. Moreover, the

surveillance-testing program should incorporate populations at risk admitted to acute care units but not necessarily to the ICU such as patients transferred from overseas or long-term-care facilities. Additionally, the program should involve screening in more than one anatomical site to increase the sensitivity of the program particularly for those on a mechanical ventilator. It is also important that the surveillance testing program include differentiation of the type of carbapenemases facilitating proper patient/staff cohorting and targeted treatment selection.

Not all CPE-colonized patients develop infections by these organisms; this study found that 30% of the CPE-colonized patients developed an infection within 7 months of colonization detection. A site of colonization that is frequently forgotten by CPE colonization-related studies is the respiratory tract; most studies rely on rectal colonization. This study found that a higher percentage of patients colonized in the respiratory tract developed infection compared to those colonized rectally or in the urinary tract; once again this highlights the importance of considering screening patients in more than one anatomical site for CRE/CPE. Similarly, the use of indwelling urinary catheters has been linked to a higher risk for infection; in this study, it was associated with a higher risk for the development of CPE infection among colonized patients. We strongly suggest implementing alternatives to the use of these devices such as condom catheters or external female catheters; daily assessment of the necessity of indwelling urinary catheters should be a regular practice at the bedside aiming to reduce not only CAUTI, but also CPE infections.

In addition, this study evaluated the duration of CPE-carriage finding a median time for clearance of 80 days; moreover, long-term carriage was detected for up to 42 months. The findings of this study indicate that discontinuation of contact precautions for CPE should be evaluated on a case-by-case basis as suggested by European guidelines. This evaluation should at least 80 days after carriage detection and should include more than one negative surveillance culture as well as agreement with the original site of carriage; it should also take into account the presence of risk factors such as exposure to carbapenems, or mechanical ventilators.

This study also found a higher risk for the development of CPE infection among colonized patients that were exposed to intravenous colistin. Similarly, the study found long-term CPE carriage associated with exposure to carbapenem. Increasing early detection of CRE/CPE has effects in rapid antimicrobial stewardship interventions that promote the appropriate selection of antibiotics preventing unnecessary exposures to carbapenems and preserving the limited available options for treatment of these organisms. Interdisciplinary approaches that incorporate infection prevention, antimicrobial stewardship, and microbiology teams are pivotal in controlling the spread of CRE/CPE globally.

Treatment and management of CRE/CPE continue to be challenging for healthcare facilities in the US. This dissertation project unveils several opportunities for future research. During the study period, new antibiotic combinations such as ceftolozane-tazobactam or ceftazidime-avibactam were not widely available; future studies should look at the effect of exposures to these antibiotics in the development of CPE infections

among colonized patients as well as in long-term CPE carriage. New studies should also evaluate the effect of interventions aimed to reduce the time to appropriate therapy in the duration of carriage and in controlling the spread of CRE/CPE.

In this study we did not include interventions such as selective decolonization or fecal transplantation for CPE colonization management; more studies are necessary that include such interventions and investigate its role in duration of CPE carriage. Prospective studies can also evaluate the effect of disrupting the gut microbiome in the development of CPE infections among colonized patients as well as in duration of CPE carriage.

Most of the carbapenemases identified in this project were KPC, with little or no representation of other ones such as NDM, VIM, or OXA; these results did not allow for comparisons of duration of CPE carriage among different carbapenemases. Larger studies are necessary that allow for such comparisons. Some carbapenemases might be more common among other Gram-negative bacilli such as *Pseudomonas;* studying other carbapenemase-producing organisms might bring a different insight to the management of extensively drug-resistant organisms in the healthcare setting.

Lastly, similar studies can evaluate epidemiological trends, risks for development of infections among colonized patients, and duration of carriage related to other emergent multidrug resistant organism such as *Candida auris,* carbapenem-resistant *Acinetobacter,* or *Clostridioides difficile*. These multidrug resistant organisms are also considered urgent threats by the CDC and are of increasing concern because of their rapid spread around the world.

VITA

ADRIANA JIMENEZ

Born, Bogotá, Colombia

1987-1992	BS, Bacteriology and Clinical Laboratory Universidad Colegio Mayor de Cundinamarca Bogotá, Colombia
1993-1998	Medical Technologist SAMU Colombian Red Cross, Bogotá, Colombia
2003-2006	MPH, Master in Public Health Florida International University Miami, Florida
2004-2011	Medical Technologist – Laboratory Specialist Baptist Health of South Florida
2011-present	Infection Prevention and Control Specialist/ Administrator Jackson Health System Miami, Florida
2014–2020	Doctoral Student/Candidate Florida International University Miami, Florida

PUBLICATIONS AND POSTERS/PRESENTATIONS (Selected)

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