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A Multi-Centered Case-Case-Control Study of Factors Associated with *Klebsiella pneumoniae* Carbapenemase-Producing Enterobacteriaceae Infections in Children and Young Adults

Latania K. Logan, MD, MSPH^{1,3,9,12}, David C. Nguyen, MD^{1,2}, Felicia A. Scaggs Huang, MD^{1,*}, Nadia K. Qureshi, MD⁵, Angella Charnot-Katsikas, MD⁶, Allison H. Bartlett, MD, MS⁷, Xiaotian Zheng, MD, PhD⁸, Andrea M. Hujer, BS^{9,11}, T. Nicholas Domitrovic, MS^{9,11}, Steven H. Marshall, MS^{9,11}, Robert A. Bonomo, MD^{9,10,11}, and Robert A. Weinstein, MD^{2,4,12}

¹Department of Pediatrics

²Department of Medicine

³Section of Pediatric Infectious Diseases

⁴Division of Infectious Diseases, Rush University Medical Center, Rush Medical College Chicago, IL

⁵Pediatrics, Loyola University Medical Center, Maywood, IL

⁶Department of Pathology

⁷Department of Pediatrics, Section of Infectious Diseases, The University of Chicago Medicine, Chicago, IL

⁸Ann and Robert H. Lurie Children's Hospital, Northwestern University Feinberg School of Medicine, Chicago, IL

⁹Louis Stokes Cleveland Veterans Affairs Medical Center

¹⁰Departments of Pharmacology, Molecular Biology, and Microbiology, Biochemistry, and Proteomics and Bioinformatics

¹¹Department of Medicine, Case Western Reserve University, Cleveland, OH

¹²Cook County Health and Hospitals System, Chicago, IL

Abstract

Background: *Klebsiella pneumoniae* carbapenemase (KPC)-producing Enterobacteriaceae (KPC-CRE) are multidrug-resistant organisms (MDRO) causing morbidity and mortality worldwide. KPC-CRE prevalence is increasing in pediatric populations, though multi-centered

Corresponding Author: Latania K. Logan, Rush University Medical Center 1653 W. Congress Parkway, Suite 951 Jelke, Chicago, IL 60612; Phone 312-942-8928; Fax: 312-942-9108; Latania_Logan@rush.edu.

*Current affiliation: Pediatric Infectious Diseases, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

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data are lacking. Identifying risk factors for KPC-CRE infection in children and classifying genotypes is a priority in this vulnerable population.

Methods: A case-case-control study of patients (0–22 years) at 3 tertiary-care Chicago-area medical centers, 2008–2015, was conducted. Case group 1 children possessed KPC-CRE infections; case group 2 harbored carbapenem-susceptible *Enterobacteriaceae* (CSE) infections; control had negative cultures. Case-control matching was 1:1:3 by age, infection site, and hospital. Statistical and molecular analyses were performed.

Results: Eighteen KPC-CRE infections were identified; median patient age was 16.5 years. Of 4 available KPC-CRE, two were unrelated, non-ST258 KP strains harboring *bla*_{KPC-2}, one was a ST258 KP harboring *bla*_{KPC-3}, and the last was an *E. coli* containing *bla*_{KPC-2}. KPC-CRE and CSE-infected patients had more MDRO infections, long-term care facility admissions, and lengths of stay (LOS) >7 days before culture. KPC-CRE and CSE patients had more gastrointestinal (GI) comorbidities (ORs 28.0 and 6.4) and 3 comorbidities (ORs 15.4 and 3.5) compared to controls; KPC-CRE patients had significantly more pulmonary and neurologic comorbidities (both ORs 4.4) or GI and pulmonary devices (ORs 11.4 and 6.1). Compared to controls, CSE patients had more prior fluoroquinolone use (OR 7.4); KPC-CRE patients had more carbapenem or aminoglycoside use (ORs 10.0 and 8.0). Race, gender, LOS, and mortality differences were insignificant.

Conclusions: Pediatric patients with KPC-CRE infection suffer from high multi-system disease/device burdens and exposures to carbapenems and aminoglycosides. Different from adult reports, non-ST258 KP strains were more common, and LOS and mortality rates were similar in all groups. Pediatric CRE control should focus on modifiable risk factors including antibiotic and device utilization.

Keywords

Epidemiology; Gram-negative bacteria; *Enterobacteriaceae* infections; carbapenemases; drug resistance; children

Introduction

Infections due to multi-drug resistant organisms (MDROs) are associated with significant morbidity and mortality and are an increasing global public health threat. The current “superbugs” – carbapenem-resistant *Enterobacteriaceae* (CRE) – are a major contributor to these increasing trends in adult patients.

In *Enterobacteriaceae*, β -lactamase (*bla*) genes on mobile genetic elements encode for a rapidly expanding list of β -lactam hydrolyzing enzymes.¹ Many *bla*-harboring *Enterobacteriaceae* carry additional plasmid-borne genes rendering them multi-drug resistant (MDR).² Few antibiotics capable of treating MDR *Enterobacteriaceae* infections are available to clinicians; consequently, carbapenems, a “last line” of therapy, are now being more and more challenged by the increasing threat of, carbapenemase-producing *Enterobacteriaceae* (CPE).³

In the United States, the epidemic of CRE infections in adults is primarily due to ST258 *Klebsiella pneumoniae* (KPC) strains carrying *bla*_{KPC-2} and *bla*_{KPC-3}.⁴ Risk factors for

KPC-CRE in adults include critical illness, prolonged hospitalization, residence in long-term care facilities, multiple invasive medical devices, comorbid conditions, poor functional status, mechanical ventilation, and receipt of certain antibiotic classes.^{5, 6, 6, 7, 7} Though risk of CRE infection is increasing in U.S. children, little is known about the epidemiology of KPC-CRE in children.^{8, 9} The majority of published pediatric studies are single centered and/or report risk factors of CRE infection in children due to multiple or undetermined mechanisms of resistance.^{10–16} In adults factors and outcomes associated with CRE infection vary by specific strains and gene types contributing to carbapenem resistance (CR) patterns.⁶

To address this challenge, we describe factors associated with KPC-CRE infections and classify genotypes of infecting strains in children cared for in three hospitals located within the same geographic area. Understanding the clinical and molecular epidemiology of KPC-CRE infections in children will have a substantial effect on infection control measures, clinical practice, and public health policies in a vulnerable population.

Methods

Study Setting

Hospital A contains a 125-bed children's hospital – general pediatrics and newborn infant, neonatal, and pediatric intensive care units – within an academic medical center. Hospital B is a 155-bed children's hospital within an academic medical center. Hospital C is a 288-bed academic free-standing children's hospital. Both Hospitals B and C provide complex quaternary pediatric care, including solid organ and stem cell transplantation services. All the participating centers are located within the same geographic area. The annual patient admissions for the institutions combined is approximately 19,250.

This study included patients 0 to 21.99 years of age found to have a positive culture for an Enterobacteriaceae with a carbapenem-resistant phenotype due to a suspected carbapenemase. Infections were diagnosed between January 1, 2008 and December 31, 2014, and only the first infection per patient was included. The study was approved by the institutional review boards of the three participating institutions and need for informed consent was waived.

Study Design

A retrospective, case–case–control study design was used as previously described¹⁷ in order to circumvent limitations of case–control studies and to best assess risk factors specifically related to infection with the KPC-CRE phenotype. Two separate analyses were performed within the study. The first comparison was between the resistant bacterial phenotype of interest (KPC-CRE) and uninfected control patients. Control patients were representative of the source population and had cultures collected within the same time period as the cases, but whose cultures were sterile. The second comparison was between patients with infections due to susceptible species of the organisms of interest and the same uninfected control patients. Comparison of the two models allowed identification of specific factors associated with the resistance phenotype of interest (i.e., KPC-CRE).¹⁷

Specifically, the first case group in this study comprised pediatric patients infected with KPC-CRE from any site. The second case group included pediatric patients with carbapenem-susceptible Enterobacteriaceae infections at the same hospital and same site of organism isolation. For cases, only infected patients (not colonized patients) were included, and infection versus colonization was determined by study investigator case review using previously published criteria of the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) as appropriate.¹⁸ Control subjects were pediatric patients identified via electronic laboratory records (ELRs) with sterile cultures during the study time period. Controls were matched 3:1 to each of the 2 cases by age range and specimen source. Control patients were distinct patients from those included in either case group.¹⁹

Covariates

Variables were analyzed as potential factors associated with KPC-CRE infection based on known associations for acquisition in adults and factors associated with resistant infections in pediatric patients including (1) demographics (age, gender, race/ethnicity); (2) comorbid conditions (as defined by ICD-9 codes); (3) length of hospital stay prior to culture; (4) premature birth, defined as less than 37 weeks gestation; (5) recent healthcare exposures, including hospitalization and/or procedures in the previous 30 days; (6) all recent antibiotic exposures in the 40 days prior to culture; (7) immunosuppressive therapy, including steroid exposure, in the 30 days prior to culture; (8) mechanical ventilation status; (9) presence, number, and type of invasive medical devices; (10) history of any prior multi-drug resistant infection ; (11) residence in long-term care facility . Clinical outcome measures evaluated included length of hospital stay after culture and mortality within the study period.

Statistical Analysis

Firstly, the three groups were assessed for differences using chi-squared tests for categorical, and analysis of variance for continuous, variables. When significant differences were discovered, Fisher's exact test and Wilcoxon rank sum tests were performed to assess which pairs of groups were different. $P < 0.05$ was considered statistically significant unless otherwise specified. Multivariable analysis was not performed due to small sample size of identified KPC-CRE infection. Analyses were performed in SAS 9.4 (SAS Institute, Cary, NC, USA).

Bacterial isolates and antibiotic susceptibility testing

CR isolates were considered to have a carbapenemase phenotype by the Centers for Disease Control and Prevention criteria if they were resistant to all expanded-spectrum cephalosporins (ceftriaxone, cefotaxime, and ceftazidime) and nonsusceptible to one or more carbapenems (ertapenem, meropenem, imipenem, or doripenem).²⁰ The presence of KPC production was phenotypically assessed by positive Modified Hodge Test (MHT), using previously validated methods,²¹ negative MBL E-test and confirmed by polymerase chain reaction (PCR) as appropriate.

Molecular Analysis

For available strains, genomic DNA was purified (DNeasy blood and tissue kit, Qiagen, Inc. Valencia, CA) and PCR and DNA Microarray (Check-MDR CT103XL; Check-Points, Wageningen, Netherlands) was performed to assess for the presence of *bla* genes in isolates as previously described and according to manufacturer protocol^{22–24}. Repetitive-sequenced based PCR (rep-PCR) was performed using the DiversiLab Strain typing system (bioMérieux, Athens, GA) and multilocus sequence typing (MLST) [Pasteur website (<http://www.pasteur.fr/recherche/genopole/PF8/mlst/>)], in addition DNA sequencing identified *bla*_{KPC} alleles in the CRE strains of *Escherichia coli* and *Klebsiella pneumoniae* as previously described.^{22, 25}

Results

Eighteen cases of Enterobacteriaceae infection, identified as KPC producers, occurred in pediatric patients ages 0–21 years of age from the three medical centers during the study period (Table 1). The majority of KPC-CRE were *K. pneumoniae* (89%) compared to a more even distribution of *K. pneumoniae* and *E. coli* in the CSE group (44% and 33%, respectively). Differences in the source of infection between groups was not observed. The antimicrobial susceptibility testing (AST) results of KPC-CRE are shown in Table 2. The highest retained overall susceptibilities were to tetracycline, gentamicin and amikacin. Notably, the KPC-CRE isolates were all MDR (resistant to 3 antibiotic classes).

The median age of KPC-CRE cases was 16.5 years of age (range 1.3 to 21.9 years), 50% were of black race, and 44% were in the pediatric intensive care unit (PICU) at the time of the infection. Significant differences in age, race or hospital setting between the 3 groups were not evident. However, both KPC-CRE and CSE groups were more likely to have a history of MDRO infections (100% of KPC-CRE children had this history) and/or a history of residence in a long-term care facility compared with controls. KPC-CRE-infected pediatric patients were also significantly more likely to have a history of recurrent infections compared to the other groups (Table 3).

Of the four KPC-CRE available for molecular analysis (three *K. pneumoniae* and one *E. coli*), none were found to be genetically related. Two KPC-producing *K. pneumoniae* strains were of non-CG258 clonal groups and included ST22 and ST29, and the KPC-producing *E. coli* was a novel ST701 type; all of which harbored a *bla*_{KPC-2}. The fourth strain was a ST258 *K. pneumoniae* that harbored a *bla*_{KPC-3}.

On bivariate analysis (Table 4), pediatric patients infected with KPC-CRE were more likely to have a hospital-acquired infection (OR 5.8, 95% CI 1.5–22.4), and less likely to have a community-acquired infection (OR 0.08, 95% CI 0.004–1.3) when compared to controls. Factors associated with KPC-CRE infection included carbapenem (OR 10.0, 95% CI 1.7–57) and aminoglycoside administration (7.96, 95% CI 2.0–32.0); length of stay (LOS) > 7 days before infection onset; the presence of respiratory or gastrointestinal medical devices (foreign bodies); more than one foreign body; and gastrointestinal (GI), pulmonary, neurologic, and multiple (>3) comorbidities. Although both GI comorbidity and aminoglycoside use were strongly associated with KPC-CRE infection, on stratified

analysis, there was evidence of negative outcome effect modification, i.e., the strength of the association of GI comorbidity on the outcome of KPC-CRE infection was less in the presence of aminoglycoside use (OR 13.5, 95% CI 3.28–55.8, $p<0.001$).

For pediatric patients with CSE infections, factors associated with infection included fluoroquinolone use (OR 7.4, 95% CI 1.2–44.8), GI and multiple comorbidities, and LOS >7 days before culture. Differences between healthcare, hospital or community onset infection types between CSE and controls were not observed.

A descriptive analysis of pediatric patients with KPC-CRE infections who had neurologic and pulmonary comorbidities was performed, as the association with these conditions was unique to the KPC-CRE case group. Of the nine pediatric patients with neurologic comorbidities, the median age was 17.4 years of age (11.2–21.9 years) and 56% were male. All KPC-CRE infections from urinary sources occurred in patients with neurologic conditions, none of which were associated with indwelling genitourinary catheters. Only one patient (11%) had an ICD-9 diagnosis of neurogenic bladder. Other associated diagnoses included 22% with cerebral palsy or paralysis, 22% with seizure disorder, 11% with history of cerebrovascular accident and 11% with history of subdural hematoma. One (always a tracheostomy) or more foreign bodies were present in 67% of cases.

All pulmonary comorbid cases ($n=10$) also had a foreign body present and in 70% of cases these were tracheostomies. Tracheostomy dependent respiratory failure was the most common diagnosis in this group (70%); one of the cases with tracheostomy also had a diagnosis of asthma. Other pulmonary comorbidities included bronchopulmonary dysplasia (20%) and pulmonary fibrosis related to autoimmune disease (10%).

GI comorbidities were associated with infection in both KPC-CRE and CSE groups. Short gut syndrome was a more common diagnosis in the KPC-CRE than in the CSE group (36% vs 11%). The majority of KPC-CRE and CSE infections in patients with GI comorbidities (86% and 67%, respectively) were also associated with GI foreign bodies, of which, gastrostomy tubes were the most common in both KPC-CRE and CSE groups (67% in each group).

As a group, pediatric patients with KPC-CRE infection had significant and complex medical histories. An example is the case of KPC-CRE infection that was associated with mortality. The patient was a 16-year-old female with neurologic and pulmonary comorbidities, a history of refractory systemic lupus erythematosus, multiple thrombi, and pulmonary fibrosis who was originally admitted for fevers, headache, nausea, emesis, and diarrhea. She had a long and complex inpatient course that included pediatric ICU admission for hypotension; history of line-related sepsis from *Candida*, methicillin-resistant *Staphylococcus aureus* and *Enterococcus*; subdural hematoma; intubation for ARDS; pneumothorax; and persistent mucositis leading to poor oral intake requiring parenteral nutrition supplementation. At the time of the urinary tract infection with KPC-producing *K. pneumoniae*, the patient had been hospitalized for 95 days and was persistently febrile. She died from cardiac arrest two days after the KPC-CRE was isolated.

Discussion

In this study, a case-case-control study design was used to identify factors associated with KPC-CRE infection in pediatric patients and to describe outcomes associated with these MDRO infections in pediatric patients in three medical centers. We additionally linked resistance phenotypes with the genetic determinants of carbapenem resistance in available isolates and assessed strain relatedness. This unique analysis allowed for an important status report of the clinical and molecular epidemiology of this emerging problem in pediatric patients.

To our knowledge, this analysis is the first to use a case-case-control design to assess factors associated with KPC-CRE infection and outcomes in pediatric patients. The study design allows differentiation of factors specific to the resistance mechanism of interest, factors associated with Enterobacteriaceae infections (both the resistant and susceptible phenotypes), and factors specific to the carbapenem susceptible phenotype.¹⁷ Use of this design also allowed us to best identify specific risk factors associated with KPC-CRE infection.

The number of subjects was similar to other U.S. pediatric studies on CRE,^{11, 13, 15, 26} represents the largest U.S. pediatric study specifically analyzing KPC-CRE to date, and is the only multicentered study on CRE infection in pediatric patients cared for at distinct institutions located in the same metropolitan area.

Similar to data from adults, we found that critical illness, invasive medical devices, comorbid conditions, mechanical ventilation, and receipt of certain antibiotic classes (e.g., carbapenems) were associated with KPC-CRE infection; and that the predominant organism harboring *bla*_{KPC} is *K. pneumoniae*. However, we did not find KPC-CRE infection to be specifically associated with residence in long-term care facilities (CSE cases had similar history of residence); conversely certain comorbidities (e.g. neurologic) and antibiotic exposures (e.g., aminoglycosides) may be particular to pediatric patients.

In adults, KPC-CRE infection has been associated with poor outcomes, with significant morbidity and mortality rates as high as 50% reported.^{6, 27} Our results did not indicate that worse outcomes occur in pediatric patients with KPC-CRE infections, as length of stay after infection and mortality were similar in both case groups and controls. Reported outcomes in other pediatric studies have been mixed, perhaps due to differences in patient populations studied

Notably, significant differences in the molecular epidemiology of isolates recovered from pediatric patients were observed. In U.S. adults, the predominant circulating KPC-CRE strains are most often ST258 *K. pneumoniae* strains harboring a *bla*_{KPC-2} or *bla*_{KPC-3} gene.⁶ Although the numbers are small in our analysis which limits the ability to draw conclusion, *bla*_{KPC} harboring *K. pneumoniae* were mainly non CG258, and the *E. coli* harboring a *bla*_{KPC-2} was a novel ST701 type. Why might this occur? We posit that: *i*) the acquisition of KPC-CRE in pediatric patients differs from adults in that it has a polyclonal epidemiology and is associated with acquisition of *bla*_{KPC} harboring plasmids circulating in the pediatric healthcare setting; and *ii*) pediatric patients are being colonized or infected much later in the

epidemic-after the *bla_{KPC}* gene and the accompanying transposons have already disseminated into different genetic environments. Pediatric studies in the U.S. which characterized KPC-CRE colonization and infection in single center settings, where circulating *bla_{KPC}* harboring strains were primarily non-ST258 and of multiple ST types, support these hypotheses.^{11, 12} From the standpoint of infection prevention measures, where the interventions differ to control spread of plasmid-related dissemination of carbapenemase genes between Enterobacteriaceae as opposed to spread due to specific clonal strains, the critical nature of these observations mandates further investigation.^{3, 7, 28}

Acknowledging that this is a retrospective study design with a relatively small sample size in a single metropolitan area, selection bias and lack of impact generalizability may be present. Nevertheless, the pooling of data from three centers serving diverse populations and environments lessened this bias. Similarly, the small sample size limited the study power and thus any meaningful interpretation by stratified or multivariable logistic regression analysis. . Despite this, the current study represents the largest study of KPC-CRE infections in U.S. pediatric patients to date. We also used a case-case-control design in an effort to overcome known limitations of case-control study design when assessing risk factors associated with resistant organisms. We may not have captured all outpatient antibiotic data, as some records were based on patient report, which is susceptible to recall bias. Isolates were collected based on phenotypic resistance suggestive of carbapenemase production; therefore, strains that possessed *bla_{KPC}* expressed at low levels may not have been identified. In addition, few isolates were available for molecular analysis, which also affects generalizability; however, our results were supported by other pediatric studies with similar findings of non-ST258 *K. pneumoniae* predominant strains harboring *bla_{KPC}*.

In conclusion, our study represents the first multicentered U.S. study of KPC-CRE infections in pediatric patients cared for in acute-care pediatric facilities within a single metropolitan area. We found that the epidemiology of KPC-CRE in pediatric patients is complex and diverse, and factors and outcomes associated with KPC-CRE infection and circulating strain types may differ from adult populations in an area where such infections are endemic. This study also highlights the unique challenges that are faced when determining strategies to control the spread of KPC-CRE infection in pediatric patients, in whom diverse and novel strain types of carbapenemase genes warrant multifaceted interventions with a focus on modifiable risk factors such as antibiotic and device utilization.

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Table 1.

Characteristics of *Klebsiella pneumoniae* Carbapenemase-producing Enterobacteriaceae (KPC-CRE) and Carbapenem-Sensitive Enterobacteriaceae (CSE)

	KPC-CRE (n=18) [†]	CSE (n=18) [†]	Control (n=54) [†]
Species n (%)			
<i>Klebsiella pneumoniae</i>	16 (89)	8 (44)	–
<i>Escherichia coli</i>	1 (5.6)	6 (33)	
<i>Enterobacter cloacae</i>	1 (5.6)	1 (5.6)	–
Other Enterobacteriaceae	0 (0)	3 (16.7)	–
Source n (%)			
Urine	4 (22)	5 (28)	19 (35)
Respiratory	4 (22)	4 (22)	11 (20)
Blood	4 (22)	5 (28)	22 (41)
Other ^b	6 (33)	4 (22)	2 (3.7)

[†]There were no significant differences for sources in cases and controls

^{†*}Other includes wound, abscess, abdominal and peritoneal sources

Table 2

Anatomical sites of isolation and antibiotic susceptibility patterns of *Klebsiella pneumoniae* carbapenemase-producing Enterobacteriaceae

Anatomical Site [†]	No. of isolates [‡]	% susceptible (no. susceptible/no. available for testing) [‡]													
		CTX	CAZ	FEP	P/T	CPM	ERT	GNT	TOB	AMK	FQ	TMP-SMX	TET	NIT	ATN
All	18	0	0	0	18 (2/11)	11	0	72	11	71 (12/17)	23 (3/13)	5.6	75 (6/8)	0 (0/4)	0 (0/8)
Urine	4	0	0	0	25	25	0	75	0	33 (1/3)	0 (0/3)	0	100 (1/1)	0	0
Respiratory	5	0	0	0	0 (0/2)	0	0	100	0	60	0	0	100 (3/3)	ND	0 (0/1)
Blood	4	0	0	0	0 (0/2)	0	0	50	0	100	0 (0/1)	0	50 (1/2)	ND	ND
Abd/Perit	3	0	0	0	100 (1/1)	33	0	33	33	100	100 (2/2)	0	100 (1/1)	ND	0 (0/2)
SST	2	0	0	0	0 (0/1)	0	0	100	50	50	50	50	0 (0/1)	ND	0 (0/1)

[†]Respiratory includes bronchoalveolar lavage fluid, trachea, sputum cultures. “Abd/Perit” includes intraabdominal and fluid peritoneal fluid cultures. SST = skin and soft tissue infections, including abscess and wound

[‡]Susceptibility data not available for all antibiotics for all isolates. [‡] CTX, ceftriaxone; CAZ, ceftazidime; FEP, cefepime; P/T, piperacillin-tazobactam; CPM, carbapenem (includes meropenem or imipenem); ERT, erapenem; GNT, gentamicin; TOB, tobramycin; AMK, amikacin; FQ, fluoroquinolones (includes ciprofloxacin and levofloxacin); TMP-SMX, trimethoprim-sulfamethoxazole; TET, tetracycline; NIT, nitrofurantoin; ATN, aztreonam; ND, no data

Table 3.

Demographic Information and Infection History for Children with *Klebsiella pneumoniae* Carbapenemase-Producing Enterobacteriaceae (KPC-CRE) and Carbapenem-Sensitive Enterobacteriaceae (CSE) Compared to Controls

	KPC-CRE (n=18)	CSE (n=18)	Control (n=54)
Age, median, y (range)	16.5 (1.26 – 21.9)	16.0 (3.82 – 21.9)	14.0 (1.10 – 21.9)
Male, n (%)	11 (61)	8 (44)	30 (56)
Race			
Black	9 (50)	9 (50)	28 (52)
Hispanic	3 (17)	2 (11)	10 (19)
White	4 (22)	7 (39)	10 (19)
Other	2 (11)	0 (0)	3 (5.6)
Unknown	0 (0)	0 (0)	3 (5.6)
History of MDRO [†]	18 (100)	2 (11)	0 (0)
Recurrent Infection [†]	7 (39)	0 (0)	1 (1.9)
Hospital Setting			
Pediatric ICU	8 (44)	7 (39)	19 (35)
Emergency Department	1 (5.6)	0 (0)	11 (20)
Pediatric Ward	7 (39)	10 (56)	22 (41)
Adult ICU	1 (5.6)	1 (5.6)	2 (3.7)
Clinic	1 (5.6)	1 (5.6)	0 (0)
Past LTCF residence ^a	4 (22)	3 (17)	0 (0)

[†] p- value significant (p <0.05) for both KPC vs control and CSE vs control in history of MDRO infection, recurrent infection, and long-term care facility (LTCF) residence.

Table 4.

Bivariate Analysis of Factors associated with *Klebsiella pneumoniae* carbapenemase-Producing Enterobacteriaceae (KPC-CRE) and Carbapenem-Sensitive Enterobacteriaceae (CSE) Versus Culture-Negative Controls

	KPC-CRE (n=18) vs Control (n=54)				CSE (n=18) vs Control (n=54)			
	Cases	Control	OR (95% CI)	P-Value	Cases	Control	OR (95% CI)	P-Value
Variable	n (%)	n (%)			n (%)	n (%)		
Infection Onset								
Healthcare Associated Infection	3 (17)	15 (28)	0.52 (0.13–2.06)	0.53	4 (22)	15 (28)	0.74 (0.21–2.62)	0.76
Hospital Acquired Infection	15 (83)	25 (46)	5.8 (1.5–22.4)	0.007	9 (50)	25 (46)	1.16 (0.40–3.37)	0.78
Community Onset Infection	0 (0)	14 (26)	0.08 (0.004–1.33)	0.015	5 (28)	14 (26)	1.10 (0.33–3.64)	0.88
Risk Factors								
Recent antibiotics	14 (78)	26 (48)	3.77 (1.10 – 12.9)	0.03	9 (50)	26 (48)	1.08 (0.37 – 3.13)	0.89
Recent penicillin	4 (22)	9 (16.7)	1.43 (0.38–5.36)	0.72	2 (11)	9 (17)	0.62 (0.12 – 3.21)	0.57
Recent 3 rd generation cephalosporin	7 (39)	17 (31.5)	1.38 (0.46–4.19)	0.57	5 (28)	17 (31)	0.84 (0.26– 2.73)	0.77
Recent carbapenem	5 (28)	2 (3.7)	10.0 (1.74–57.4)	0.009	1 (5.6)	2 (3.7)	1.53 (0.13–17.9)	0.74
Recent fluoroquinolone	2 (11)	2 (3.7)	3.25 (0.42–25.0)	0.26	4 (22)	2 (3.7)	7.43 (1.23–44.8)	0.031
Recent aminoglycoside	7 (39)	4 (7.4)	7.96 (1.98 – 32.0)	0.004	0 (0)	4 (7.4)	0.30 (0.02–5.91)	0.23
Recent TMP-SMX	3 (16.7)	5 (9.3)	1.96 (0.42– 9.18)	0.40	1 (5.6)	5 (9.3)	0.58 (0.06 – 5.29)	0.63
Recent steroids	5 (28)	13 (24)	1.21 (0.36–4.05)	0.76	5 (28)	13 (24)	1.21 (0.36–4.04)	0.75
Recent procedure	6 (33)	14 (26)	1.43 (0.45–4.53)	0.54	8 (44)	14 (26)	2.29 (0.75–6.94)	0.14
Foreign body present	15 (83)	29 (54)	4.31 (1.12–16.6)	0.029	8 (44)	29 (54)	0.69 (0.26–2.01)	0.50
CVL	10 (56)	17 (31.5)	2.72 (0.91–8.11)	0.07	4 (22)	17 (31.5)	0.62 (0.18 – 2.17)	0.56
Respiratory	11 (61)	11 (20)	6.14 (1.93–19.5)	0.001	5 (28)	11 (20)	1.50 (0.44–5.12)	0.52
Trach	7 (39)	2 (3.7)	16.5 (3.0 – 90.6)	<0.001	3 (17)	2 (3.7)	5.20 (0.79–34.0)	0.10
Mechanical ventilation	6 (33)	12 (22)	1.75 (0.54–5.65)	0.35	3 (17)	12 (22)	0.70 (0.17–2.83)	0.75
Gastrointestinal	13 (72)	10 (18.5)	11.4 (3.31 – 39.5)	<0.001	6 (33)	10 (18.5)	2.20 (0.67–7.28)	0.19
Genito-urinary	5 (28)	5 (9.3)	3.77 (0.95–15.0)	0.11	2 (11)	5 (9.3)	1.23 (0.21–6.94)	0.82
>1 foreign bodies present	12 (67)	14 (26)	5.71 (1.80–18.1)	0.004	5 (28)	14 (26)	1.10 (0.33–3.64)	0.88
Comorbidities								
Cardiovascular	2 (11)	2 (3.7)	3.25 (0.42–25.0)	0.26	2 (11)	2 (3.7)	3.25 (0.42–25.0)	0.26
Gastrointestinal	14 (78)	6 (11)	28.0 (6.9–113.3)	0.0001	8 (44)	6 (11)	6.40 (1.82 – 22.5)	0.002
Pulmonary	9 (50)	10 (18.5)	4.40 (1.39–13.9)	0.009	6 (33)	10 (18.5)	2.20 (0.66 – 7.28)	0.21

	KPC-CRE (n=18) vs Control (n=54)				CSE (n=18) vs Control (n=54)			
	Cases	Control	OR (95% CI)	P-Value	Cases	Control	OR (95% CI)	P-Value
Variable	n (%)	n (%)			n (%)	n (%)		
Neurologic	9 (50)	10 (18.5)	4.40 (1.39–13.9)	0.009	7 (39)	10 (18.5)	2.80 (0.88 – 9.02)	0.11
Hematology-Oncology	10 (56)	16 (30)	2.97 (0.99 – 8.9)	0.05	4 (22)	16 (30)	0.68 (0.19–2.38)	0.55
Renal	5 (28)	7 (13)	2.58 (0.70 – 9.49)	0.14	3 (17)	7 (13)	1.34 (0.31–5.85)	0.70
Rheumatology	3 (17)	3 (5.6)	3.40 (0.62–18.6)	0.16	1 (5.6)	1 (5.6)	1.00 (0.10 – 10.3)	1.00
>3 Comorbidities	14 (78)	10 (18.5)	15.4 (4.17–56.9)	0.001	8 (44)	10 (18.5)	3.52 (1.11 – 11.2)	0.03
LOS before culture > 7 days	5 (22)	4 (7.4)	4.81 (1.13–20.4)	0.038	6 (33)	4 (7.4)	6.25 (1.52–25.7)	0.013
Survived	16 (89)	54 (100)	0.06 (0.003–1.33)	0.01	16 (89)	54 (100)	0.06 (0.003–1.33)	0.013
LOS after culture > 7 days	10 (56)	20 (37)	2.1 (0.72–6.27)	0.17	8 (44)	20 (37)	1.36 (0.46 – 4.01)	0.58