Emergence of carbapenemase-producing *Klebsiella pneumoniae* of sequence type 258 in Michigan, USA

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Abstract

The prevalence of carbapenemase-producing Enterobacteriaceae (CPE) in our hospital increased beginning in 2009. We aimed to study the clinical and molecular epidemiology of these emerging isolates. We performed a retrospective review of all adult patients with clinical cultures confirmed as CPE by positive modified Hodge test from 5/2009- 5/2010 at the University of Michigan Health System (UMHS). Clinical information was obtained from electronic medical records. Available CPE isolates were analyzed by polymerase chain reaction (PCR) and sequencing of the 16S rRNA encoding gene and bla_{KPC} locus. Multilocus sequence typing (MLST) was used to characterize *Klebsiella pneumoniae* isolates. Twenty six unique CPE isolates were obtained from 25 adult patients. The majority were *Klebsiella pneumoniae* (n=17). Other isolates included *K. oxytoca* (n=3), *Citrobacter freundii* (n=2), *Enterobacter cloacae* (n=2), *Enterobacter aerogenes* (n=1) and *Escherichia coli* (n=1). Molecular characterization of 19 available CPE isolates showed that 13 (68%) carried the KPC-3 allele and 6 (32%) carried the KPC-2 allele. Among 14 available *K. pneumoniae* strains, 12 (86%) carried the KPC-3 allele and belonged to a common lineage, sequence type (ST) 258. The other 2 (14%) *K. pneumoniae* isolates carried the KPC-2 allele and belonged to two unique STs. Among these ST 258 strains, 67% were isolated from patients with prior exposures to health care settings outside of our institution. In contrast, all CPE isolates carrying the KPC-2 allele and all non ST 258 CPE isolates had acquisition attributable to our hospital.

Molecular epidemiology of carbapenemase producing *K. pneumoniae* suggests that KPC-3 producing *K. pneumoniae* isolates of a common lineage, sequence type (ST 258), are emerging in our hospital. While ST 258 is a dominant sequence type throughout the United States, this study is the first to report its presence in Michigan.

Introduction

Antibiotic resistance presents a significant risk for patients and healthcare providers. The global dissemination of multidrug resistant bacteria limits the utility of commonly used antimicrobials. Infections caused by these organisms are increasing in health care settings, posing challenges to clinical microbiology laboratories in rapidly identifying resistant organisms, to clinicians in choosing appropriate antimicrobial treatments and to infection preventionists in implementing effective infection control interventions.

Carbapenems have become the treatment of choice for serious infections by gram negative hospital associated pathogens including extended-spectrum β-lactamase (ESBL) producing Enterobacteriaceae.[1] Increased use of carbapenems has been predictably followed by the arrival of carbapenem resistance. Carbapenem resistance in Enterobacteriaceae has been largely due to acquisition of carbapenemase genes belonging to Ambler classes A, B and D β-lactamases.[2] *Klebsiella pneumoniae* carbapenemases (KPCs) are the most common plasmid encoded Class A carbapenamases. In recent years, many variants of KPC genes (bla_{KPC}) have been reported.[3] Carbapenemase producing Enterobacteriaceae (CPE) have emerged as important nosocomial pathogens and spread globally with a marked endemicity in the eastern United States, Israel, and Greece.[4,5] Among healthcare associated infections reported to the Centers for Disease Control and Prevention, 8% of *Klebsiella* isolates were carbapenem resistant in 2007 compared to fewer than 1% in 2000.[6] A particular clonal lineage of carbapenemase producing *Klebsiella pneumoniae*, sequence type (ST) 258, has been commonly associated with outbreaks in many countries,[7,8] suggesting that this epidemic clone may have contributed to spread of the bla_{KPC} genes.[9,10] Although CPE isolates are endemic to southeastern Michigan,[11] the presence of *K. pneumoniae* ST 258 in Michigan has not been previously reported. Beginning in 2009, we observed an increased prevalence of CPE in our hospital. At the time of publication, approximately 7% of *K. pneumoniae* isolates in our hospital are carbapenem resistant compared to only sporadic carbapenem resistant isolates prior to 2009.[12] The purpose of this study was to investigate the clinical and molecular epidemiology of CPE isolates and to identify possible clonal spread of CPE in our hospital.

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Materials and Methods

This study was conducted at the University of Michigan Health System (UMHS), a 925 bed teaching hospital with 100 adult ICU beds and 44,000 annual inpatient discharges. Following UMHS Institutional Review Board approval, we retrospectively identified all adult patients from May 2009 through May 2010 with clinical cultures positive for CPE. Clinical information

including patient demographics, co-morbidities, health care exposures (invasive devices, antibiotics, prior hospitalization or stay in long term care facilities) in the 90 days prior to culture, current hospitalization length of stay, antimicrobial treatment, and 90 day mortality outcomes were abstracted from electronic medical records. CPE isolates were considered hospital acquired (nosocomial to UMHS) if the culture was obtained 48 hours or more after admission to UMHS unless there was evidence of prior CPE isolation from the same patient at another hospital. Appropriate treatment was defined as the administration of at least one antibiotic to the patient that demonstrated *in vitro* activity against the infecting CPE isolate. When carbapenem resistance was identified by the clinical microbiology laboratory, patients were placed in contact precautions and charts were electronically flagged in case of readmission. If a patient was transferred to other health care facilities, the status was conveyed to the accepting facility. However due to the retrospective nature of the study, molecular testing results were not available and were not reported to other institutions.

CPE isolates were identified by the UMHS clinical microbiology laboratory based upon phenotypic and antimicrobial susceptibility testing of Enterobacteriaceae using the Vitek-2 system (bioMérieux, Durham, NC). Isolates with ertapenem MIC ≥2 mg/L were subjected to ertapenem disc diffusion testing. If the zone of inhibition was ≤22 mm, then the modified Hodge test was performed to phenotypically confirm carbapenemase production in accordance with Clinical and Laboratory Standard Institute (CLSI) criteria.[13] Only CPE isolates confirmed by positive modified Hodge test were included in the study.

Bacterial DNA was extracted from overnight Mueller-Hinton broth cultures of CPE isolates using the Easy-DNA™ Kit (Invitrogen-Carlsbad, CA). The taxonomy of all available isolates was determined by amplification and sequencing of the 16S rRNA encoding gene, followed by BLAST (Basic Local Alignment Search Tool) querying the National Center for Biotechnology Information (NCBI) nucleotide database (http://blast.ncbi.nlm.nih.gov/Blast.cgi). Briefly, broad range primers (8F and 1492R) were used to amplify ~1493 base pair region of the 16S rRNA encoding gene with high-fidelity taq polymerase (AmpliTaq Gold Master Mix, Applied Biosystems, Inc).[14] Reaction mixtures were set up with 1 µL of template DNA (approximately 100 ng), 10 pmol of each primer, master mix, and water to a total volume of 25 µL. PCR was performed in Eppendorf Master cycler thermocycler with the following cycling conditions: initial denaturation at 95°C for 5 min followed by 35 cycles of denaturation at 95°C for 30 seconds, annealing at 58°C for 30 seconds, and extension at 72°C for 1.5 min. A final extension at 72°C for 10 min was performed. Amplicons were purified (QIA quick PCR Purification Kit, Qiagen, Inc) and sequenced bi-directionally (forward and reverse directions) using standard Sanger-style sequencing on an ABI 3730XL capillary sequencer. Raw sequences were trimmed, aligned, and edited using the SeqMan II program of the DNASTAR Lasergene 7 package (DNASTAR, Inc., Madison, WI) and consensus sequences were submitted to BLAST. All taxonomic identifications were at least 99% identical to representative sequences in the NCBI database. Allelic variants of the bla_{KPC} gene were identified using methods published by Bradford *et al*.[15] Multilocus sequence typing (MLST) was performed to characterize *K. pneumonia*e genotypes as described on the K. *pneumoniae* MLST website (http://www.pasteur.fr/recherche/genopole/PF8/mlst/Kpneumoniae.html). Briefly, internal fragments of seven housekeeping *loci* were amplified and sequenced at 2x coverage (*i.e*. each nucleotide site was covered twice). Raw sequences were trimmed, aligned, and edited using SeqMan II and consensus reads were compared using MEGA5.[16] *K. pneumonia*e sequence types were identified by searching allele profiles of the *K. pneumoniae* MLST website.

Results

Twenty six unique CPE isolates including *K. pneumoniae* (n=17), *K. oxytoca* (n=3), *Citrobacter freundii* (n=2), *Enterobacter cloacae* (n=2), *Enterobacter aerogenes* (n=1), and *Escherichia coli* (n=1) were obtained from 25 adult patients. In one patient *E.coli* and *K. pneumoniae* were sequentially isolated one month apart during the same admission. Isolates were cultured from urine (n=15), respiratory tract (n=8), blood (n=5), and wound (n=3) samples. Among the 26 unique isolates, 18 (69.2%) were resistant to trimethoprim/sulfamethoxazole, 16 (61.5%) to ciprofloxacin, 14 (53.8%) to gentamicin and tobramycin and 1 (3.8%) to amikacin. Susceptibility to colistin and tigecycline was not routinely performed on all isolates however when tested 0% (0/7) were resistant to colistin and 37.5% (6/16) were resistant to tigecycline. Some CPE isolates also expressed resistance profiles consistent with ESBL (38%), or AmpC (23%) production on phenotypic testing (Table 1).

Patients had multiple co-morbidities including hypoalbuminemia (72%), anemia (64%), renal insufficiency (56%), history of transplant (28%) including 7 solid organ (3 livers, 1 heart/renal, 1 heart and 1 renal) and one stem cell transplant and malignancy (24%) (Table 2). The majority of patients were exposed to health care environments in the 90 days prior to CPE isolation including prior hospitalization (92%), prior ICU stay (60%), prior abdominal procedures or surgeries (56%) as well as invasive devices; indwelling urinary catheters (92%), central venous catheters (80%), and mechanical intubation (64%). Eight (32%) patients had a prior history of stay in long term care (LTCF) or long term acute care (LTAC) facilities. The mean hospital length of stay from admission to positive culture was 21.6 days (median 6, range 0-127). Acquisition was attributed to our hospital in 15 (60%) patients. Twenty-two patients (88%) received appropriate treatment for CPE infection and the mean total length of hospital stay was 49.4 days (median 21, range 0-215 days). Four (16%) patients died within 90 days following initial CPE isolation, including one (20%) following CPE bacteremia and in-hospital mortality occurred in 2 patients (8%). Among the patients who survived hospitalization, 13 (52%) were discharged to LTCFs or LTACs, 2 (8%) transferred to other hospitals and only 8 (32%) were discharged home (Table 2).

Table 1. Resistance to non-beta lactam antibiotics among Carbapenem Producing Enterobacteriaceae isolates.

Antibiotics	Resistant n (%)
Trimethoprim/sulfamethoxazole	18 (69.2)
Ciprofloxacin	16 (61.5)
Gentamicin	14 (53.8)
Tobramycin	14 (53.8)
Amikacin	1 (3.8)
Colistin	0 (0)*
Tigecycline	6 (37.5)**

*7 isolates tested for colistin susceptibility, **16 isolates tested for tigecycline susceptibility.

Among 26 unique CPE isolates, 19 were available for molecular characterization. Based on 16S rRNA sequencing, the majority of the CPE isolates were *K. pneumoniae* (n=14), followed by *K. oxytoca* (n=2), *E. coli* (n=1), *Enterobacter hormaechei* (n=1) and *C. freundii* (n=1). 16S rRNA sequencing results were discrepant from Vitek-2 system identification in 2 cases: *K. oxytoca* (Vitek) identified as *K. pneumoniae* (16S) and *E. cloacae* (Vitek) identified as *E. hormaechei* (16S). Results of 16S rRNA were given precedence over Vitek-2 identification for molecular epidemiology. Isolates carried either bla_{KPC} allele 3 (KPC-3; n=13) or allele 2 (KPC-2; n=6). Twelve of 14 *K. pneumoniae* isolates (86%) were KPC-3. All *K. pneumoniae* isolates carrying the KPC-3 allele were ST 258 when analyzed by MLST (Figure 1). The other two (2/14) *K. pneumoniae* isolates carried KPC-2 alleles and belonged to two different STs. These STs are not currently in the online *K. pneumoniae* MLST database due to a novel *tonB* allele in one case and a novel combination of previously reported alleles in the

second. In one patient *E. coli* and *K. pneumoniae* were sequentially isolated one month apart and both isolates carried the KPC-2 allele. Of the 19 CPE isolates characterized here, 11 (58%) were considered to be acquired at UMHS, which included 6/6 (100%) expressing KPC-2 and 5/13 (38.5%) expressing KPC-3 strains. Of the 12 ST 258 *K. pneumoniae* isolates, only 4 (33%) were considered nosocomial to UMHS. The ST 258 strains were significantly more likely to be isolated from patients who were exposed to non-UMHS health care facilities, including other hospitals (2 strains; 16.7%) or long term care facilities (6 strains; 50%) within the 90 days prior to CPE isolation (P=0.0065). In contrast, all 7 non-ST 258 CPE isolates were nosocomial to UMHS.

Discussion

The CPE population at our institution has a unique molecular epidemiology. Notably, all non-ST 258 CPE isolates were considered nosocomial to our institution. These isolates were taxonomically diverse (Figure 1) and with a single exception (*E. hormaechei*) all carried the KPC-2 allele. A previous study from our hospital showed evidence of a common KPC-2 carrying plasmid among two genera of Enterobacteriaceae.[12] Recently other studies have shown evidence of horizontal transfer of bla_{KPC}-carrying plasmids across different strains, species and genera of family Enterobacteriaceae.[17-19] Similarly, carriage of the KPC-2 gene by two unique isolates belonging to different genera from the same patient in our study could also be due to horizontal intergenus plasmid transfer which has been described previously.[17-19] Further studies including plasmid and transposons characterizations are required on our isolates to support this hypothesis. While 60% of CPE patients had prior ICU stay within the prior 90 days and 92% had prior hospitalization within the prior 90 days, we were unable to identify any epidemiological link among patients with nosocomial acquisition of CPE in our hospital.

All 12 ST 258 *K. pneumoniae* isolates found at our institution carried the KPC-3 allele and among these, 67% were isolated from patients with prior exposures to health care settings outside of our institution. While all KPC-2 CPE isolates and all non ST 258 CPE isolates had acquisition attributable to our hospital, only 33% of ST 258 *K. pneumoniae* isolates were considered to have acquisition attributable to our hospital. This suggests that the ST 258 lineage is not yet endemic at our institution but is circulating in the surrounding geographical region.[8] These results have important implications in understanding regional dissemination of CPE isolates and highlight the likely role of the frequent transfer of patients among multi-

Table 2. Clinical characteristics of patients with carbapenemase producing enterobacteriaceae (n=25).

Patient demographics	n (%)
Mean age (years)	61.8 (median 63, range 22-80)
Gender (male)	15 (60)
Patient comorbidities	
Hypoalbuminemia*	18 (72)
Anemia°	16 (64)
Renal insufficiency#	14 (56)
Diabetes	12 (48)
History of transplant	6 solid organ + 1 stem cell transplant (28)
History of malignancy	6 (24)
Admission source	
Admitted from home	17 (68)
Transferred from other hospitals	7 (28)
Transferred from LTCF/LTAC	1 (4)
Specimen source	
Urine	15 (60)
Respiratory tract	8 (32)
Blood	5 (20)
Wound	3 (12)
Primary service at the time of culture	
Surgery	13 (52)
Medicine	12 (48)
ICU at time of CPE culture	9 (36)
Exposure to health care environments prior to CPE culture	
Hospitalization in past 90 days	23 (92)
ICU in past 90 days	15 (60)
Stay in LTCF/LTAC in past 90 days	8 (32)
Presence of devices (90 days) prior to CPE culture	
Urinary catheter	23 (92)
Central venous catheter	20 (80)
Mechanical ventilation	16 (64)
Antibiotic within 90 days prior to culture	
Piperacillin/Tazobactam	16 (64)
Vancomycin	16 (64)
Cephalosporins	15 (60)
Quinolones	8 (32)
Carbapenems	7 (28)
Mean length of stay (days)	
Prior to CPE culture	21.6 (median 12, range 0-127)
Total	49.4 (median 21, range 5-215)
Nosocomial to UMHS§	15 (60)
Isolates nosocomial to UMHS according to molecular epidemiology (n=19)	
KPC-2 (n=6)	6 (100)
KPC-3 (n=13)	5 (38.5)
ST 258 (n=12)	4 (33)
Appropriate treatment^	22 (88)
Outcomes	
In-hospital mortality	2 (8)
3-month mortality	4 (16)
Discharge to	
Home	8 (32)
LTACF	7 (28)
LTCF	6 (24)
Other hospital	2 (8)

Unless otherwise indicated, data are number (%) where percentage is out of total number of patients. LTACF, long-term acute care facility; LTCF, long term care facility; ICU, intensive care unit. *Albumin <3.5 g/dL; °Hemoglobin <10 g/dL; #Serumcreatinine >1.5 mg/dL; §Defined as CPE isolation >48 hours of admission unless history of recent positive culture at other hospital before admission to UMHS; ^Defined as administration of *in vitro* active antibiotics against CPE.

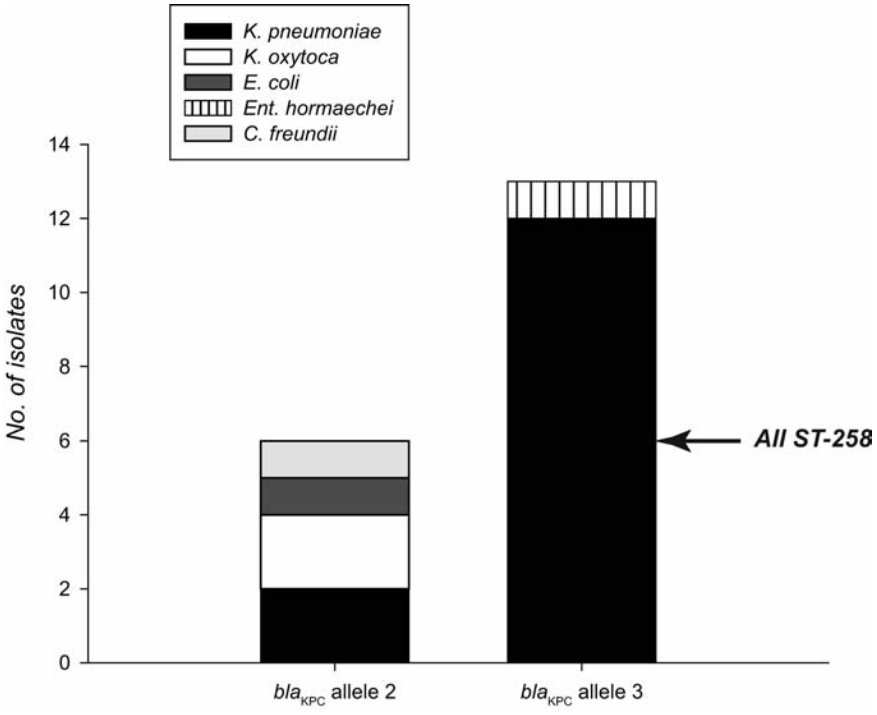

Figure 1. The number and species of CPE isolates carrying blaKPC alleles 2 or 3. All *K. pnuemoniae* isolates carrying allele 3 belonged to ST 258.

ple health care facilities in propagating cross-transmission and rapid regional spread of these bacteria.[8,11,20]

K. pneumoniae ST 258 are prevalent throughout the United States and globally,[8] but its presence in Michigan has not been previously reported. Moreover, ST 258 isolates can carry either KPC-3 or KPC-2 genes,[8] so the observation that all carbapenemase producing *K. pneumoniae* isolates at our institution carried KPC-3 genes suggests the emergence of a single clone in the region. More data from other regional health care facilities are needed to adequately address this hypothesis.

We observed an overall mortality of 16% which is lower (32-44%) than some reports.[11,21] This lower mortality may reflect the urinary source of most (58%) of our CPE isolates, as a previous study found that patients were at a decreased risk of in-hospital mortality when CPE were isolated from urine compared to other sources.[11] In addition we did not attempt to differentiate between clinical infection and colonization with CPE, which may have influenced patient mortality outcomes. However we observed lower mortality (20%) even among bacteremic patients.

The main limitation of our study was the small sample size of the CPE patient cohort and the availability of even fewer isolates for molecular analysis. Since the study design was descriptive, we were unable to identify specific risk factors or attributable mortality associated with CPE in our patients. However, our patients also had high rates of prolonged exposure to health care environments including ICUs and broad spectrum antibiotics, consistent with prior studies.[20,22,23]

Conclusions

Our data suggest the transmission of the bla_{KPC} gene in our geographic region by both clonal spread (ST 258) and potentially horizontal transfer. These complex modes of resistance transmission have significant public health and epidemiological implications.[17,24] Further studies including molecular sub typing (*e.g.* multi *locus* variable tandem number repeat analysis) and plasmid characterization are needed to understand emergence and transmission of these clones. Due to limited therapeutic options and poor outcomes associated with these resistant organisms, heightened awareness and prompt detection of CPE emergence at the institutional and regional level is necessary to direct infection control and antimicrobial stewardship efforts to limit the spread of these pathogens.

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