

Detection of KPC in *Acinetobacter* spp. in Puerto Rico[∇]

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Received 1 July 2009/Returned for modification 21 August 2009/Accepted 21 December 2009

During an island-wide PCR-based surveillance study of beta-lactam resistance in multidrug-resistant (MDR) *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter calcoaceticus-baumannii* complex isolates obtained from 17 different hospitals, 10 KPC-positive *Acinetobacter* isolates were identified. DNA sequencing of the *bla*_{KPC} gene identified KPC-2, -3, and -4 and a novel variant, KPC-10. This is the first report of a KPC-type beta-lactamase identified in *Acinetobacter* species.

The *Acinetobacter calcoaceticus-baumannii* complex has been recognized, during the last few decades, as an important opportunistic pathogen associated with life-threatening nosocomial infections and hospital outbreaks, as well as an agent of serious infections in injured U.S. military personnel returning from the Middle East war zones (9, 25, 33). In addition to their ability to survive in adverse environmental conditions (14), the organisms have intrinsic and acquired mechanisms of antimicrobial resistance, such as porin downregulation, overexpression of efflux pumps, chromosomal and plasmid-acquired beta-lactamases, aminoglycoside-modifying enzymes, and fluoroquinolones resistance, among others (11). Class B metallo-beta-lactamases and class D oxacillinase with carbapenemase activity have been identified in *Acinetobacter* species as a mechanism of broad-spectrum beta-lactam resistance (11, 20).

The molecular class A beta-lactamases of the KPC family are a group of potent carbapenemases identified initially in a *Klebsiella pneumoniae* isolate from the United States and later in other members of the *Enterobacteriaceae* family and in other geographical regions worldwide (17, 20). *Pseudomonas aeruginosa* positive for the *bla*_{KPC} gene has been recently identified in Colombia, Puerto Rico, and Trinidad and Tobago (3, 28, 29).

Up to date, eight different KPC variants (KPC-2 to -9) have been identified differing by 1 or 2 two amino acid substitutions. KPC-2 and -3 are the most common variants identified in *Enterobacteriaceae* and *P. aeruginosa*. KPC-6, -7, and -8 have been identified only in *K. pneumoniae*, while KPC-9 was detected in *Escherichia coli* and KPC-5 in *P. aeruginosa*. All the KPC variants except for KPC-7 and -9 have been detected in Puerto Rico (21–24, 29). In this report, we describe for the first time the presence of the KPC gene in clinical isolates of *Acinetobacter* species in Puerto

Rico and the identification of a novel KPC variant, KPC-10, in one of the isolates.

A PCR-based surveillance study of beta-lactam resistance was started in January 2009 in 17 hospitals across the island. After Institutional Review Board approval, the participating hospitals sent isolates of all unique, consecutive, multidrug-resistant *Acinetobacter* species with their corresponding susceptibility report and basic epidemiologic information. PCR screening with family-specific beta-lactamase primers for KPC and IMP and multiplex PCR for OXA carbapenemases and for CTX-Ms were performed as previously described (29, 31, 32). The Vitek DCS-R5 system confirmed the identification of the isolates as those in the *A. calcoaceticus-baumannii* complex. Bidirectional sequencing of the full-length *bla*_{KPC} gene PCR product was independently generated at least twice to identify the type of the KPC variant. DNA sequencing was commercially performed by Davis Sequencing. Sequence alignment and analysis were done online by utilizing the BLAST program (www.ncbi.nlm.nih.gov). Trek GNXF Gram-negative MIC plate microdilution panels (Westlake, OH) were utilized to perform antibiotic susceptibility tests by following the manufacturer's instruction, and the results were interpreted as recommended by the Clinical and Laboratory Standards Institute (8). No attempts were made to evaluate patients' therapies or clinical outcomes.

From a total of 274 multidrug-resistant *Acinetobacter* isolates collected from January to May of 2009, 10 (3.4%) were identified as KPC positive. Seven were detected in the metropolitan San Juan area, two in the north, and one in the central region of Puerto Rico.

Table 1 shows the patients' pertinent clinical information and type of KPC variants identified. There were six male and four female patients, whose average age was 69 years, ranging from 40 to 95 years. Six were isolated from patients in the intensive care units either from sputum (four isolates) or blood (two isolates) samples. The average hospital length of stay was 41.6 days (range, 11 to 96 days). Six patients had ventilator-associated pneumonia with or without sepsis. Six patients had skin and soft-tissue infections. All patients had significant comorbid conditions, such as cardiovascular, renal, neurologic, or traumatic injuries. The crude mortality rate for the 10 patients was

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[∇] Published ahead of print on 28 December 2009.

TABLE 2. MICs of 10 KPC-positive *Acinetobacter calcoaceticus-baumannii* complex isolates to selected antibiotics

Test agent ^a	Range (µg/ml)	MIC (µg/ml)															
		ClA9C9-24	M2AC9-31	M3AC9-2	M3AC9-4	M3AC9-6	M3AC9-7	MClAC9-26	MC4AC9-30	N2AC9-18	N2AC9-19	W2AC8-S10 ^d	<i>E. coli</i> ATCC 25922	<i>P. aeruginosa</i> ATCC 27853			
CTX	1-32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	4	1	16
CAZ	1-16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	2	1	2
FBP	2-16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	2	2	<2
TZP	8/4-6/4/4	>6/4/4	>6/4/4	>6/4/4	>6/4/4	>6/4/4	>6/4/4	>6/4/4	>6/4/4	>6/4/4	>6/4/4	>6/4/4	>6/4/4	>6/4/4	8/4	8/4	<8/4
DOR ^b	0.12-2	>2	>2	>2	>2	>2	>2	>2	>2	>2	>2	>2	>2	>2	0.12	0.12	0.5
IPM	1-8	4	8/1	>8	>8	>8	>8	8	8	8	8	8	8	8	1	1	2
MEM	1-8	4	8/1	>8	>8	>8	>8	8	8	8	8	8	8	8	1	1	<1
CIP	0.25-2	>2	>2	>2	>2	>2	>2	>2	>2	>2	>2	>2	>2	>2	0.25	0.25	0.25
LVX	1-8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	1	1	<1
GEN	1-8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	1	1	<1
AMK	4-32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	4	4	<4
SXT	0.5/9.5-4/7/6	>4/7/6	>4/7/6	>4/7/6	>4/7/6	>4/7/6	>4/7/6	>4/7/6	>4/7/6	>4/7/6	>4/7/6	>4/7/6	>4/7/6	>4/7/6	0.5/9.5	0.5/9.5	>4/7/6
MIN	2-16	8	<2	4	<2	<2	<2	4	4	4	4	4	4	4	2	2	16
TGC ^c	0.25-8	1	1	0.5	0.25	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	<0.25	0.25	8
CST	0.25-4	1	0.5	0.5	1	1	1	1	1	1	1	1	1	1	0.25	0.25	1
PMB	0.25-4	0.5	<0.25	<0.25	<0.25	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	1

^a CTX, cefotaxime; CAZ, ceftazidime; FBP, ceftepime; TZP, piperacillin-tazobactam; DOR, doripenem; IPM, imipenem; MEM, meropenem; CIP, ciprofloxacin; LVX, levofloxacin; GEN, gentamicin; AMK, amikacin; SXT, trimethoprim-sulfamethoxazole; MIN, minocycline; TGC, tigecycline; CST, colistin; and PMB, polymyxin B.
^b Doripenem breakpoint value obtained from Doxibax package insert.
^c No breakpoints available for *Acinetobacter* species.
^d *A. calcoaceticus-baumannii* complex strain W2AC8-S10 is a KPC-negative, OXA-51-positive susceptible isolate.

TABLE 1. Pertinent clinical information and type of KPC variants

<i>Acinetobacter</i> isolate	Hosp ^a	Hosp unit ^b	Geographic area	Sample site	Age (yr)	Gender ^c	Date of (mo/day/yr):		Length of stay (days)	Related	Diagnosis ^e		Outcome	KPC variant	PCR OXA ^f
							Admission	Specimen collection			Other	Other			
MClAC9-26	MCl	Gen ward	Metro ^g	Blood	73	M	3/11/09	3/22/09	38	VAP, sepsis, UTI	AMI, ARF, RF, ICH	Death	KPC-3	51	
MC4AC9-30	MC4	ICU	Metro	Sputum	40	M	3/14/09	4/7/09	54	VAP, UTI, skin abscess	Gun-shot wound	Discharge	KPC-2	51	
M3AC9-2	M3	Gen ward	Metro	Urine	68	F	1/19/09	1/19/09	9	Skin ulcer	CV/A, dementia	Death	KPC-3	51	
M3AC9-4	M3	ICU	Metro	Sputum	73	F	1/6/09	1/22/09	96	VAP, UTI, skin Ulcer	AMI, CVA, RF	Discharge	KPC-3	51	
M3AC9-6	M3	ICU	Metro	Blood	52	M	12/27/08	1/28/09	32	VAP, sepsis	CHF, CRF	Death	KPC-3	51	
M3AC9-7	M3	ICU	Metro	Blood	58	F	1/18/09	2/7/09	74	Catheter sepsis	DVT, osteomyelitis	Discharge	KPC-3	51	
M2AC9-31	M2	Gen ward	Metro	Skin wound	95	M	3/23/09	3/24/09	11	Skin ulcer	Dementia, seizures	Discharge	KPC-4	51	
N2AC9-18	N2	ICU	North	Sputum	58	M	3/5/09	4/2/09	49	VAP, sepsis, skin ulcer	RF	Death	KPC-3	51	
N2AC9-19	N2	Gen ward	North	Skin	88	M	3/30/09	4/1/09	14	Skin ulcer	Gastric CA, anemia	Discharge	KPC-3	51, 58	
ClAC9-24	Cl	ICU	Central	Sputum	88	F	3/20/09	3/31/09	39	VAP	RF, intestinal obstruction	Discharge	KPC-10	51	

^a Hosp, hospital.
^b Gen Ward, general ward; ICU, intensive care unit.
^c Metro, metropolitan area.
^d M, male; F, female.
^e VAP, ventilator-associated pneumonia; UTI, urinary tract infection; AMI, acute myocardial infarct; ARF, acute renal failure; RF, respiratory failure; ICH, intracerebral hemorrhage; CV/A, cerebrovascular accident; CHF, congestive heart failure; CRF, chronic renal failure; and DVT, deep vein thrombophlebitis.
^f OXA type found by multiplex PCR.

40%. Nine patients were treated with multiple antibiotic courses during their hospitalization (data not shown). Our patients shared similar characteristics to those described in the literature, such as significant comorbidities, prolonged hospitalizations, invasive procedures, exposure to multiple antibiotic regimens, and high crude mortality rates (1, 2, 10, 27). In our island-wide surveillance study, all hospitals with KPC-positive *Acinetobacter* isolates also had KPC-positive *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and/or *Escherichia coli* isolates (21).

The susceptibility tests shown in Table 2 showed that colistin, polymyxin B, tigecycline, and minocycline had the lowest MICs of the tested antibiotics. Resistance to quinolones, aminoglycosides, and to the beta-lactam antibiotics, including carbapenems, was observed. The therapeutic options available for the treatment of multidrug-resistant *Acinetobacter* are limited (5, 15). Our results, as well as others (4, 7, 13, 26, 34), suggested that tigecycline, polymyxins, colistin, and possibly minocycline have consistent *in vitro* activity against this organism.

The PCR results obtained with family-specific beta-lactamase primers showed that all isolates were positive for *bla*_{KPC} and *bla*_{OXA-51}-like groups and negative for *bla*_{IMP} and *bla*_{CTX-M} genes. Sequencing of *bla*_{KPC} detected the following variants: KPC-3 in seven isolates; KPC-4, KPC-2, and a novel KPC-10 (GenBank accession number GQ140348) in one isolate each. The identification of a class D *bla*_{OXA-51}-like gene in all isolates was expected, since it had been shown to be chromosomally located in *A. baumannii* (11, 20). One isolate had the *bla*_{OXA-58}-like group, which has been shown to be carried on a plasmid, recovered from diverse geographic regions, and associated with nosocomial outbreaks (6, 12, 18, 19).

To our knowledge, this is the first report of multidrug-resistant *A. calcoaceticus-baumannii* complex clinical isolates harboring the KPC gene. The presence of this gene suggests the possibility of horizontal transmission, as this carbapenemase has been associated with mobile genetic elements (transposons) which can be transferred from one bacterium to another (11, 16, 17, 30).

The presence of the *bla*_{KPC} gene in *Acinetobacter* species adds another important element to an organism already harboring multiple innate and acquired mechanisms of resistance with the real possibility of horizontal transfer of a very troublesome and potent carbapenemase. This clearly emphasizes the importance of judicious use of antibiotics and strict infection and environmental control practices in acute and chronic care facilities to reduce the possibility of nosocomial transmission and potential outbreaks.

This work was supported by Janssen Ortho-McNeil, Inc. (Johnson & Johnson); Merck Sharp and Dohme, Inc.; Pfizer, Inc.; and NCR/NIH-RCMI award G12RR03051.

We appreciate the technical assistance of Caleb Fernandez, Teresa Martínez, Iván Claudio, Yanira Rosario, Melissa Miranda, Tania Díaz, and Jennifer Pérez and also Wieslaw J. Kozek for reviewing the manuscript. We thank the following hospital medical technologists for collecting the samples and clinical information: Myriam Corazón, María Matos, Linnette Santos, Nayda Vázquez, and Abigail Torres.

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