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Notes

Emergence in Japan of an imipenem-susceptible, meropenem-resistant *Klebsiella pneumoniae* carrying bla_{IMP-6} ☆,☆☆

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Abstract

We identified 5 *Klebsiella pneumoniae* isolates showing high resistance to β-lactams except imipenem and designated them ISMRK (imipenem-susceptible but meropenem-resistant *Klebsiella*). They carried the bla_{IMP-6} and $bla_{CTX-M-2}$ on a self-transmissible plasmid. ISMRK may be falsely categorized as susceptible to carbapenems if imipenem is used to screen carbapenem resistance.
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Keywords: Carbapenem resistance; Klebsiella; Metallo-β-lactamase; ESBL

1. Introduction

In 2009, we conducted a surveillance of extended spectrum β-lactamase (ESBL)–producing *Escherichia coli* and *Klebsiella pneumoniae* from 17 general hospitals in Hiroshima. Of 2,113 isolates of *K. pneumoniae* screened, 52 isolates were ESBL-positive. Among the ESBL-positive *K. pneumoniae*, 5 isolates showed unusual resistance phenotype for carbapenems (Table 1). Clinical and epidemiological data are listed in Table 2. They were highly resistant to almost all β-lactam antibiotics except imipenem according to the criteria by the Clinical and Laboratory Standards Institute [CLSI] (2010). The MICs against meropenem were >8 μg/mL using the MicroScan system (Siemens Healthcare Diagnostics, Tokyo, Japan). Determination of the end point using the microdilution method showed that the MICs against meropenem and doripenem of 4 isolates were 32 μg/mL and 1 was 64 μg/mL (Table 2). Conversely, their MICs against imipenem were 1 μg/mL and those against panipenem and biapenem are 0.5–2 μg/mL. The data clearly showed that the 5 *K. pneumoniae* isolates were resistant to most β-lactams including meropenem and doripenem, but susceptible to imipenem, panipenem, and biapenem. Since imipenem and meropenem are the 2 most widely used carbapenems, we therefore designated these isolates as ISMRK (*i*mipenem-*s*usceptible but *m*eropenem-*r*esistant *K*lebsiella). All 5 isolates were positive in the double-disc synergy test using sodium mercaptoacetic acid (Genthner et al., 1988), indicating that the isolates produce metallo-β-lactamases

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Table 1
Antibiotic susceptibility profiles[#]

	a26*	b19	d47	d69	F22	*E. coli* BL21 Chrolamphenicol[r] (transconjugant)*	*E. coli* BL21 Chrolamphenicol[r] (recipient)*
Ampicillin	>16	>16	>16	>16	>16	>16	≦2
Piperacillin	>64	>64	>64	>64	>64	>64	≦8
Cefazolin	>16	>16	>16	>16	>16	>16	≦4
Cefotiam	>16	>16	>16	>16	>16	>16	≦8
Cefotaxime	>32	>32	>32	>32	>32	>32	≦8
Ceftazidime	>16	>16	>16	>16	>16	>4	≦1
Cefpirome	>16	>16	>16	>16	>16	>16	≦8
Cefozopran	>16	>16	>16	>16	>16	>16	≦2
Cefmetazole	>32	>32	>32	>32	>32	16	≦4
Cefaclor	>16	>16	>16	>16	>16	>16	≦8
Cefpodoxime	>4	>4	>4	>4	>4	>4	≦4
Flomoxef	32	32	32	32	32	32	≦2
Aztreonam	>16	>16	>16	>16	>16	4	≦1
Imipenem	1 (1)	1 (1)	1 (1)	1 (2)	1 (1)	1 (0.25)	≦0.5 (0.125)
Meropenem	>8 (32)	>8 (32)	>8 (32)	>8 (64)	>8 (64)	4 (2)	≦0.5 (0.02)
Amoxicillin/ clavulanate	16	16	16	16	16	4	≦2
Cefoperazone/ sulbactam	>32	>32	>32	>32	>32	32	≦4
Amikacin	≦4	≦4	≦4	≦4	≦4	≦4	≦4
Gentamicin	4	4	4	4	4	4	≦1
Minocycline	>8	>8	>8	>8	>8	≦1	≦1
Levofloxacin	>4	>4	>4	>4	>4	≦0.5	≦0.5
Fosfomycin	>16	16	16	16	16	≦4	≦4
Sulfamethoxazole/ trimethoprim	≦2	≦2	≦2	≦2	≦2	≦2	≦2

r denotes resistant.

[#] Susceptibility tests were performed using the MicroScan system panel of (μg/mL) antibiotics (Siemens). In the case of imipenem and meropenem, MIC data using broth microdilution method are listed in parentheses.

* Columns indicate MIC profiles of the donor, the transconjugant and the recipient.

(MBLs). These isolates were resistant to minocycline, levofloxacin, and fosfomycin, but susceptible to amikacin and gentamicin (Table 1). The aim of this study was to characterize resistance determinant of ISMRK.

We analyzed the genomic background of the isolates using pulsed-field gel electrophoresis (PFGE) and performed subsequent clustering analysis as described (Kouda et al., 2009). XbaI digestion of *K. pneumoniae* chromosomal DNA produced 9–14 fragments of between 10 and 600 kb. They showed a similar PFGE pattern with similarity coefficient of over 80%. Multilocus sequence typing was performed using the 5 isolates according to the method of the Institute of Pasteur (Diancourt et al., 2005) with some modifications, and all of the 5 isolates belonged to ST37.

Polymerase chain reaction (PCR) mapping (Kouda et al., 2009) of the integron of a26 followed by sequencing revealed the presence of both the $bla_{\text{IMP-6}}$ (a variant of $bla_{\text{IMP-1}}$ [A640G]) and $bla_{\text{CTX-M-2}}$ genes. The $bla_{\text{IMP-6}}$ gene was located in the variable region of a class 1 integron, just downstream of the *aac6′-Ib′* gene cassette,

Table 2
Clinical data of 5 patients infected or colonized with ISMRK and carbapenem susceptibilities of the isolates

Isolate	Hospital	In/out	Age	Sex	Date of culture	Sample	Diagnosis	Clinical outcome	Carbapenems use	MIC (μg/mL)[#]				
										IPM	MEPM	PAPM	BIPM	DRPM
a26	A	In	81	M	(2009/08/28)	Urine	Aortic dissection	Favourable	None	1	32	1	1	32
b19	B	In	92	M	(2009/10/02)	Bile	Acute cholangitis	Favourable	None	1	32	0.5	0.5	32
d47	C	In	82	F	(2009/05/28)	Urine	Cardiogenic cerebral embolism	Favourable	None	1	32	0.5	1	32
d69	C	In	90	F	(2009/11/02)	Sputum	Pneumonia	Favourable	None	2	64	4	0.5	64
f22	D	In	92	F	(2009/07/01)	Sputum	Recurrent aspiration pneumonia	Death (nonrelated)	Panipenem, doripenem	1	64	2	2	64

[#] The microdilution method was used to assess an end point for the carbapenem MIC according to the CLSI guidelines (Clinical and Laboratory Standards Institute, 2010). M = Male; F = female; IPM = imipenem; MEPM = meropenem; PAPM = panipenem; BIPM = biapenem; DRPM = doripenem.

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