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Phenotypic and Genotypic Characterization of *Enterobacteriaceae* with Decreased Susceptibility to Carbapenems: Results from Large Hospital-Based Surveillance Studies in China[▽]

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The resistance mechanism of 49 *Enterobacteriaceae* isolates with decreased susceptibility to carbapenems collected from 2004 to 2008 at 16 teaching hospitals in China was investigated. Moderate- to high-level carbapenem resistance in most isolates was more closely associated with loss or decreased expression of both major porins combined with production of AmpC or extended-spectrum β-lactamase enzymes, while KPC-2, IMP-4, and IMP-8 carbapenemase production may lead to a low to moderate level of carbapenem resistance in *Enterobacteriaceae* in China.

To date, the emergence of carbapenem-resistant *Enterobacteriaceae* has been reported in some countries (7, 9, 16, 19). Carbapenemases and porin loss combined with AmpC enzyme hyperproduction are regarded as the main mechanisms of resistance (7, 9, 12, 19). In China, there have been some reports of KPC-2-producing carbapenem-resistant *Klebsiella pneumoniae*, *Serratia marcescens*, and *Escherichia coli* in the city of Hangzhou (2, 17, 20). However, a nationwide survey has not been performed. In this study, 49 *Enterobacteriaceae* isolates with decreased susceptibility to carbapenems (MIC of imipenem, meropenem, or ertapenem of ≥2 μg/ml) were collected from 16 teaching hospitals in a nationwide distribution, which included 26 *K. pneumoniae*, 8 *E. coli*, 10 *Enterobacter cloacae*, 2 *Enterobacter aerogenes*, and 3 *Citrobacter freundii* isolates. Identification of organisms was confirmed by using the API 20E or Vitek2 Compact system (bioMérieux, France). Susceptibility testing was performed by using the agar dilution method according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI) (3, 4). Breakpoints for tigecycline were as defined by the FDA (susceptible, ≤2 μg/ml; resistant, ≥8 μg/ml). Forty-nine isolates were nonsusceptible to most antibiotics except to tigecycline (to which 45 of 49 isolates were susceptible) and polymyxin B (to which 47 of 49 isolates were susceptible).

Conjugation experiments were carried out in mixed broth cultures, as described previously (2). Plasmid DNAs of all carbapenemase-producing isolates were obtained with a QIAfilter midikit (Qiagen, Hilden, Germany). Resistance genes were successfully transferred from 23 of 49 isolates to the recipient *E. coli* C600. Among the 16 carbapenemase-producing clinical isolates, carbapenemase genes of 13 isolates were successfully transferred to *E. coli* C600, except for three IMP-4-producing *E. cloacae* isolates. The 13 carbapenemase-producing transconjugants showed 8- to 64-fold increases in the MIC of imipenem, 32- to 512-fold increases in the MIC of meropenem, and 256- to 4,096-fold increases in the MIC of ertapenem relative to those of the recipient. Most of the carbapenemase-producing transconjugants harbored a single plasmid, while only one transconjugant (GZ64T) harbored four different plasmids (Table 1).

PCR of β-lactamase genes for the transconjugants and respective donors was carried in a PTC-200 PCR system (Bio-Rad). The primers used in this study were described previously (1, 5, 11, 12, 14, 18, 19). PCR products were purified with a QIAquick PCR purification kit (Qiagen) and were sequenced on an ABI PRISM 3730XL sequencer analyzer. Carbapenemase genes were detected in 16 of 49 clinical isolates, which involved the $bla_{\text{KPC-2}}$ gene from four *K. pneumoniae* and two *E. coli* isolates, the $bla_{\text{IMP-4}}$ gene from three *K. pneumoniae*, three *E. cloacae*, and two *C. freundii* isolates, and the $bla_{\text{IMP-8}}$ gene from two *K. pneumoniae* isolates. Among 49 clinical isolates, 23 carried $bla_{\text{TEM-1}}$, 21 carried bla_{SHV}, and 26 carried $bla_{\text{CTX-M}}$, while $bla_{\text{CTX-M-14}}$ and $bla_{\text{CTX-M-3}}$ were the predominant genotypes among CTX-M-producing isolates. Fourteen isolates carried $bla_{\text{DHA-1}}$, and seven carried $bla_{\text{CMY-2}}$. Other β-lactamase genes (bla_{NMC}, bla_{SME}, bla_{IMI}, bla_{GES}, bla_{VIM}, bla_{SPM}, bla_{SIM}, bla_{GIM}, and bla_{OXA}) were not detected in any of the 49 isolates.

All 49 isolates and their transconjugants were screened for the *qnr* (*qnrA*, *qnrB*, and *qnrS*) genes by multiplex PCR (13) and for *aac(6′)-Ib-cr* by PCR and sequencing (10). Among 49 isolates, 14 carried *qnr* genes, and *qnrS1* (9/14) and *qnrB* (5/14) were the predominant *qnr* genotypes. Seventeen of 49 isolates carried an *aac(6′)-Ib* gene, and 9 of them were determined to be *aac(6′)-Ib-cr*.

Class 1 integrons were detected in the 49 clinical isolates and corresponding transconjugants by PCR and sequencing (8). Nine different structures of class 1 integrons were found in these isolates (Tables 1 and 2). The most common gene cassettes contained resistance determinants to aminoglycosides (*aadA5*, *aadA2*, and *aadA1*) and trimethoprim (*dfrA17* and

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TABLE 1. Susceptibilities and resistance mechanisms of carbapenemase-producing isolates and their transconjugants

Isolate no.[a]	Species	Site[b]	MIC (μg/ml) of drug[c]												Plasmid size(s) (kb)	Resistance mechanism(s)	Integron
			IPM	MEM	ETP	FOX	TZP	CTX	CAZ	FEP	CIP	AMK	TGC	POL			
ZJ18	*K. pneumoniae*	ZJ1	16	8	16	>256	>256	128	64	16	>32	>256	1	0.5	147, 6.4, 4.1, 3.4	KPC-2, SHV-28, DHA-1, ompK35 loss	
ZJ18T			2	1	2	128	64	8	16	4	1	>256	0.06	0.25	147	KPC-2, DHA-1	
ZJ70	*K. pneumoniae*	ZJ2	>256	256	>256	128	>256	>256	64	>256	16	>256	0.25	0.5	42, 5.2, 2.5	KPC-2, SHV-11, CTX-M-14, ompK35/36 loss	*dfrA12-orfF-aadA2*
ZJ70T			16	8	16	32	>256	64	32	32	0.13	1	0.13	0.25	42	KPC-2	
ZJ71	*K. pneumoniae*	ZJ2	16	16	16	16	>256	256	32	128	16	>256	0.13	1	42, 5.2, 2.5	KPC-2, TEM-1, SHV-11, CTX-M-14, ompK35 loss	*dfrA12-orfF-aadA2*
ZJ71T			8	4	4	32	>256	16	32	16	0.25	1	0.13	0.5	42	KPC-2	
ZJ99	*K. pneumoniae*	ZJ1	16	4	8	32	>256	128	64	32	>32	0.5	1	1	90	KPC-2, CTX-M-3, qnrS1, ompK35 DE[d]	
ZJ99T			16	16	8	32	>256	256	128	64	2	2	0.25	0.25	90	KPC-2, CTX-M-3, qnrS1	
ZJ86	*E. coli*	ZJ1	8	8	32	64	256	64	32	32	>32	1	0.25	0.5	120, 23, 7.1, 6.4, 5.9, 5.3, 3.9, 2.9, 2.3, 1.0	KPC-2, TEM-1, ompC loss	*dfrA17-aadA5*
ZJ86T			8	8	16	64	>256	32	32	16	0.25	32	0.25	0.5	120	KPC-2	
ZJ87	*E. coli*	ZJ1	8	8	16	64	256	64	32	32	>32	1	0.25	0.5	120, 23, 7.1, 5.9, 5.3, 3.9, 2.9, 2.3, 1.0	KPC-2, TEM-1, ompC loss	*dfrA17-aadA5*
ZJ87T			8	8	16	64	>256	32	32	16	0.25	1	0.25	0.25	120	KPC-2	
FZ47	*K. pneumoniae*	FZ	8	2	8	>256	64	256	>256	128	4	>256	1	1	190, 110, 80	IMP-8, TEM-1, SHV-11, CTX-M-14, qnrB2, aac(6′)-Ib, ompK35/36 loss	*dfrA12-orfF-aadA2*
FZ47T			4	1	4	>256	8	128	>256	64	1	>256	0.06	0.25	190	IMP-8, TEM-1, CTX-M-14, qnrB2, aac(6′)-Ib	*dfrA12-orfF-aadA2*
FZ49	*K. pneumoniae*	FZ	8	2	4	>256	128	>256	>256	256	0.5	>256	0.5	1	190, 110, 80	IMP-8, TEM-1, SHV-11, CTX-M-14, qnrB2, aac(6′)-Ib, ompK35/36 loss	*dfrA12-orfF-aadA2*
FZ49T			4	1	4	>256	8	128	>256	32	1	>256	0.06	0.25	190	IMP-8, TEM-1, CTX-M-14, qnrB2, aac(6′)-Ib	*dfrA12-orfF-aadA2*
GZ64	*K. pneumoniae*	GZ1	16	8	32	>256	>256	256	>256	128	2	1	0.5	0.5	140, 49, 11, 5.9, 3	IMP-4, ompK35/36 loss	*IMP-4–orfII*
GZ64T			2	2	4	256	8	128	256	16	0.25	1	0.06	0.5	140, 49, 11, 5.9	IMP-4	*IMP-4–orfII*
WH76	*K. pneumoniae*	WH	2	4	2	>256	16	128	256	32	0.5	1	0.5	1	57	IMP-4, TEM-1, SHV-14, CTX-M-3, qnrS1	
WH76T			4	8	2	>256	32	256	>256	64	2	1	0.06	0.5	57	IMP-4, TEM-1, CTX-M-3, qnrS1	
WH77	*K. pneumoniae*	WH	2	4	4	>256	32	256	256	32	0.5	1	0.5	1	57	IMP-4, TEM-1, SHV-14, CTX-M-3, qnrS1	
WH77T			4	4	4	>256	32	256	>256	64	2	1	0.06	0.5	57	IMP-4, TEM-1, CTX-M-3, qnrS1	
SZ62	*C. freundii*	SZ	4	4	4	>256	256	256	>256	64	32	>256	1	0.5	48, 33, 5.5, 5.4, 4.2, 3.3, 2.8, 1.7, 1.2	IMP-4, TEM-1, CMY-2, qnrS1, aac(6′)-Ib-cr	
SZ62T			4	4	4	>256	32	128	>256	32	4	1	0.13	0.25	48	IMP-4, qnrS1	

SZ63	*C. freundii*	SZ	4	4	4	>256	>256	>256	>256	128	32	>256	1	0.5	171, 48, 33, 6.8, 5.5, 5.4, 4.2, 3.3, 2.8, 1.7, 1.2	IMP-4, qnrS1	*dfrA12-orfF-aadA2*
SZ63T			4	4	4	>256	32	256	>256	64	2	>256	0.13	0.5	171, 48	IMP-4, qnrS1	*dfrA12-orfF-aadA2*
SZ92	*E. cloacae*	SZ	8	8	32	>256	128	>256	>256	128	>32	1	1	0.5	55, 7, 5.9, 5.5, 4.9, 2.5, 1.1	IMP-4, TEM-1, CTX-M-14, DHA-1, qnrB10/B4-like, aac(6′)-Ib, ompC loss	*orfx-aac6′-II, aadA1*
RJ94	*E. cloacae*	RJ	8	8	32	>256	256	>256	>256	256	4	0.5	1	0.5	98, 48	IMP-4, TEM-1, CTX-M-3, ompC loss	*PSE-1*
WH103	*E. cloacae*	WH	8	8	32	>256	>256	>256	>256	>256	32	1	1	0.5	118, 51	IMP-4, TEM-1, CTX-M-3, qnrS1, ompC loss	*dfrA12-aadA2*
C600	*E. coli*		0.25	0.03	0.008	16	1	0.13	0.5	0.06	0.25	1	0.06	0.5			

[a] *E. coli* C600 was the recipient; T at the end of the isolate number indicates the transconjugant.
[b] FZ, The Affiliated Union Hospital of Fujian Medical University; GZ1, The First Affiliated Hospital of Zhongshan University; RJ, The Affiliated Ruijin Hospital of Shanghai Jiaotong University; SZ, Shenzhen People's Hospital; WH, The Affiliated Tongji Hospital of Huazhong University of Science and Technology; ZJ1, The First Affiliated Hospital of Zhejiang University; ZJ2, The Second Affiliated Hospital of Zhejiang University.
[c] IPM, imipenem; MEM, meropenem; ETP, ertapenem; FOX, cefoxitin; TZP, piperacillin-tazobactam; CTX, cefotaxime; CAZ, ceftazidime; FEP, cefepime; CIP, ciprofloxacin; AMK, amikacin; TGC, tigecycline; POL, polymyxin B.
[d] DE, decreased expression.

dfrA12). *K. pneumoniae* strain GZ64 gave a 2.2-kb PCR amplicon for class 1 integrons that contained bla_{IMP-4} and orfII (putative reverse transcriptase gene).

Pulsed-field gel electrophoresis (PFGE) typing was performed as described previously (15), and it showed that *K. pneumoniae* ZJ70 and ZJ71 (from Hangzhou), *E. coli* ZJ86 and ZJ87 (from Hangzhou), and *C. freundii* SZ62 and SZ63 (from Shenzhen) were clonally related.

Outer membrane proteins (OMPs) were isolated by sarcosyl extraction of total membrane preparations as described previously (6). Expression levels of the two corresponding major porins (OmpK35 and OmpK36 for *K. pneumoniae* and OmpF and OmpC for *E. coli*, *E. cloacae*, *E. aerogenes*, and *C. freundii*) were investigated. Thirty-three of 49 isolates, including 19 *K. pneumoniae* and 14 other *Enterobacteriaceae*, lost or had lower expression of both major porins, while 12 isolates lost or had lower expression of one porin. Expression of both major porin proteins was normal in only four isolates. Isolates with a combination of carbapenemase and porin loss showed relatively high carbapenem MICs (*K. pneumoniae* strains ZJ70 and ZJ71). Among the 33 non-carbapenemase-producing isolates, 29 showed loss or lower expression of both major porins, and 28 produced extended-spectrum β-lactamases (ESBLs), AmpC, or both types of enzymes simultaneously (Tables 2 and 3). The MIC ranges of imipenem, meropenem, and ertapenem against these 28 isolates were 2 to 32 μg/ml (20 imipenem-resistant isolates with MICs of ≥16 μg/ml), 2 to 16 μg/ml (9 meropenem-resistant isolates with MICs of 16 μg/ml), and 16 to 128 μg/ml (all resistant to ertapenem), which is relatively higher than those of the isolates with single porin loss (Table 3).

In this study, 16 of 49 isolates produced KPC-2 or IMP-4/8 carbapenemases. *K. pneumoniae* was the most frequently isolated carbapenemase-producing species (9/16 isolates) and produced KPC-2, IMP-4, and IMP-8 carbapenemases. IMP-4 was the most common carbapenemase type in this study (8/16) and was found in *K. pneumoniae*, *E. cloacae*, and *C. freundii*. KPC-2 has emerged in China but was limited to certain areas, such as the city of Hangzhou. Importantly, this study showed that two-thirds of carbapenemase-nonsusceptible isolates (33/49) did not produce carbapenemases, and most of these isolates (28/33) had lost or had reduced expression of both major porin proteins (OmpK35/36 or OmpF/C), usually in combination with ESBL production (23/28; mainly CTX-M-14, SHV-11, and CTX-M-3) or AmpC (17/28; DHA-1 and CMY-2). This indicated that loss or decreased expression of both of the major porins may play an important part in an increased resistance level to carbapenems. AmpC or ESBL production may contribute to the resistance level among these isolates. These data suggest that the high prevalence rates of ESBLs and AmpC among *Enterobacteriaceae* may predispose these organisms to carbapenem resistance.

Nucleotide sequence accession numbers. The sequences of the carbapenemase genes in this study were submitted to GenBank and assigned accession numbers EU368858 (bla_{IMP-4} harbored by *K. pneumoniae*), EU368857 (bla_{IMP-4} harbored by *C. freundii*), EU368856 (bla_{IMP-8} harbored by *K. pneumoniae*), and EU244644 (bla_{KPC-2} harbored by *K. pneumoniae*).

TABLE 2. Susceptibilities and resistance mechanisms of non-carbapenemase-producing isolates with porin loss and their transconjugants

Isolate no.[a]	Species	MIC (μg/ml) of drug[b]												Resistance mechanism(s)	Integron
		IPM	MEM	ETP	FOX	TZP	CTX	CAZ	FEP	CIP	AMK	TGC	POL		
CY1	*K. pneumoniae*	32	16	32	>256	8	128	256	64	>32	>256	16	1	SHV-11, DHA-1, ompK35/36 loss	*dfrA12-orfF-aadA2*
CY1T		0.25	0.016	0.008	64	2	4	64	1	2	>256	1	0.25	SHV-11, DHA-1	*dfrA12-orfF-aadA2*
PU3	*K. pneumoniae*	32	16	64	>256	>256	128	128	64	>32	16	0.25	0.5	DHA-1, aac(6′)-Ib-cr, ompK35/36 loss	
PU4	*K. pneumoniae*	16	4	32	>256	8	16	64	0.5	>32	>256	4	0.5	SHV-1, DHA-1, ompK35/36 loss	
PU5	*K. pneumoniae*	16	8	64	>256	256	>256	256	256	>32	>256	0.5	1	SHV-12, DHA-1, aac(6′)-Ib-cr, ompK35/36 loss	
PU8	*K. pneumoniae*	16	8	32	>256	128	128	256	4	>32	8	1	1	SHV-11, DHA-1, aac(6′)-Ib-cr, ompK35/36 loss	
SZ61	*K. pneumoniae*	16	8	64	>256	>256	128	256	16	>32	>256	4	0.5	TEM-1, SHV-1a, CMY-2, ompK35/36 loss	
GZ66	*K. pneumoniae*	32	4	64	>256	>256	128	>256	32	>32	>256	0.5	0.5	SHV-11, DHA-1, ompK35/36 loss	*aadA2*
GZ66T		0.5	0.032	0.008	128	1	16	128	1	1	>256	0.125	0.25	SHV-11, DHA-1	
SX67	*K. pneumoniae*	4	2	32	>256	>256	>256	>256	256	>32	>256	0.5	1	SHV-2, CTX-M-14, DHA-1, qnrB6/S1, aac(6′)-Ib-cr, ompK35/36 loss	
CY75	*K. pneumoniae*	32	8	64	>256	>256	>256	256	2	>32	2	1	1	SHV-11, DHA-1, ompK35/36 loss	
XJ81	*K. pneumoniae*	8	2	64	>256	>256	>256	>256	256	1	16	0.5	0.5	TEM-1, SHV-12, DHA-1, aac(6′)-Ib, ompK35/36 loss	*dfrA12-orfF-aadA2*
XJ81T		0.25	0.016	0.008	16	2	4	64	0.5	0.125	16	0.064	0.25	TEM-1, SHV-12, aac(6′)-Ib	
PU105	*K. pneumoniae*	32	16	128	>256	>256	>256	>256	128	>32	>256	2	32	TEM-1, SHV-12, CTX-M-14, DHA-1, qnrB10/B4-like, aac(6′)-Ib-cr, ompK35/36 loss	
ZJ68	*K. pneumoniae*	4	8	64	32	>256	>256	256	>256	4	>256	0.125	1	CTX-M-15, ompK35/36 loss	*dfrA12-orfF-aadA2*
ZJ68T		0.5	0.032	0.064	16	32	>256	256	128	0.125	>256	0.064	0.5	CTX-M-15	*dfrA12-orfF-aadA2*
ZJ69	*K. pneumoniae*	32	4	32	>256	16	64	128	8	32	>256	0.5	1	SHV-28, ompK35/36 loss	
GZ83	*K. pneumoniae*	32	8	128	>256	>256	>256	>256	32	>32	>256	0.5	1	SHV-11, CTX-M-14, ompK35/36 loss	*aadA2*
PU104	*K. pneumoniae*	2	8	64	256	>256	>256	>256	>256	4	0.5	0.5	0.5	TEM-1, SHV-11, CTX-M-15, qnrS1, ompK35/36 loss	
PU104T		0.25	0.032	0.016	256	4	256	64	32	0.25	2	0.25	0.25	TEM-1, CTX-M-15	
PU60	*E. coli*	32	8	64	>256	256	256	256	16	>32	32	0.125	0.5	TEM-1, CMY-2, ompC/F loss	*dfrA17-aadA5*
PU60T		0.5	0.032	0.064	128	4	16	64	0.5	0.25	1	0.125	0.25	CMY-2	
PU96	*E. coli*	32	8	128	>256	>256	>256	>256	64	>32	2	1	0.5	TEM-1, CTX-M-14, CMY-2, ompC/F loss	
PU101	*E. coli*	32	16	128	>256	>256	>256	>256	64	>64	4	0.064	0.5	TEM-1, CTX-M-14, CMY-2, ompC loss, ompF DE[c]	
PU101T		0.25	0.032	0.25	>256	32	128	>256	1	0.25	1	0.25	0.25	CMY-2	
PU102	*E. coli*	16	8	64	>256	>256	>256	64	>256	>64	64	0.25	0.5	TEM-1, CTX-M-14, CMY-2, aac(6′)-Ib, ompC DE[c], ompF loss	*dfrA17-aadA5*
PU102T		0.25	0.032	0.25	>256	>256	256	64	64	0.25	1	0.25	0.25	TEM-1, CTX-M-14, CMY-2	
GX24	*E. cloacae*	4	2	16	>256	>256	256	>256	1	8	>256	1	2	TEM-1, DHA-1, aac(6′)-Ib, ompC loss, ompF DE[c]	*dfrA12-orfF-aadA2*[c]
PU41	*E. aerogenes*	32	8	64	>256	128	>256	64	256	8	>256	1	0.5	CTX-M-14, DHA-1, qnrS1, ompC DE[c], ompF loss	
PU41T		0.5	0.032	0.032	256	1	128	64	16	2	>256	0.064	0.25	CTX-M-14, DHA-1, qnrS1	
PU43	*E. coli*	8	16	32	128	256	>256	32	>256	>32	8	0.25	0.5	TEM-1, CTX-M-14, aac(6′)-Ib, ompC/F loss	*cmlA1* variant-like–*aac(6′)-Ib*
HX74	*E. coli*	4	8	16	64	>256	>256	256	>256	>32	8	0.064	0.5	TEM-1, CTX-M-14, CTX-M-3, aac(6′)-Ib-cr, ompC/F loss	*dfrA17-aadA5*
HX74T		0.25	0.064	0.064	16	4	>256	256	256	0.25	2	0.125	0.25	CTX-M-3	
GX56	*E. cloacae*	4	4	32	>256	>256	>256	256	>256	>32	>256	4	0.5	ompC loss, ompF DE[c]	*dfrA12-orfF-aadA2*
WH85	*E. aerogenes*	8	8	16	256	>256	>256	32	>256	0.032	1	0.064	0.5	TEM-1, CTX-M-3, ompC/F loss	
NJ88	*E. cloacae*	16	16	128	>256	128	>256	>256	>256	16	>256	0.5	0.5	CTX-M-14, ompC/F loss	
NJ89	*E. cloacae*	16	16	128	>256	128	>256	>256	>256	16	>256	0.5	0.5	CTX-M-14, ompC/F loss	
NJ90	*E. cloacae*	16	16	128	>256	128	>256	>256	>256	16	>256	0.5	0.5	CTX-M-14, ompC/F loss	
NJ91	*E. cloacae*	16	16	128	>256	128	>256	>256	>256	16	>256	0.5	0.5	CTX-M-14, ompC/F loss	
GZ84	*K. pneumoniae*	1	1	8	>256	>256	256	256	32	>32	16	0.5	0.5	SHV-11, aac(6′)-Ib-cr, ompK35 loss	
WH97	*K. pneumoniae*	2	2	4	>256	32	128	>256	32	1	1	0.5	0.5	SHV-33, aac(6′)-Ib, ompK35 DE	
RJ78	*C. freundii*	8	2	8	>256	>256	256	128	64	16	8	1	2	CMY-2, qnrA1, aac(6′)-Ib-cr, ompC loss	
SZ93	*E. cloacae*	4	0.125	0.064	>256	2	1	0.5	0.125	0.064	1	1	>32	ompC loss	
C600	*E. coli*	0.25	0.032	0.008	16	1	0.125	0.5	0.064	0.25	1	0.064	0.5		

[a] *E. coli* C600 was the recipient; T at the end of the isolate number indicates the transconjugant.

[b] IPM, imipenem; MEM, meropenem; ETP, ertapenem; FOX, cefoxitin; TZP, piperacillin-tazobactam; CTX, cefotaxime; CAZ, ceftazidime; FEP, cefepime; CIP, ciprofloxacin; AMK, amikacin; TGC, tigecycline; POL, polymyxin B.

[c] DE, decreased expression.

TABLE 3. Distribution and corresponding carbapenem MIC ranges for strains with different resistance determinants

Resistance determinant profile	No. of isolates	MIC (μg/ml) range		
		Imipenem	Meropenem	Ertapenem
IMP-4$^+$, no porin loss or decreased expression	4	2–4	4	2–4
IMP-4$^+$, single porin loss	3	8	8	32
IMP-4$^+$, double porin loss	1	16	8	32
KPC-2$^+$, single porin loss or decreased expression	5	8–16	4–16	8–32
KPC-2$^+$, double porin loss	1	>256	256	>256
IMP-8$^+$, double porin loss	2	8	2	4–8
Carbapenemase$^-$, ESBL$^+$, AmpC$^-$, single porin loss or decreased expression	2	1–2	1–2	4–8
Carbapenemase$^-$, ESBL$^+$, AmpC$^-$, double porin loss	11	2–32	4–16	16–128
Carbapenemase$^-$, ESBL$^-$, AmpC$^+$, single porin loss	1	8	4	8
Carbapenemase$^-$, ESBL$^-$, AmpC$^+$, double porin loss or decreased expression	5	4–32	2–16	16–64
Carbapenemase$^-$, ESBL$^+$, AmpC$^+$, double porin loss or decreased expression	12	4–32	2–16	32–128
Carbapenemase$^-$, ESBL$^-$, AmpC$^-$, single porin loss	1	4	0.125	0.064
Carbapenemase$^-$, ESBL$^-$, AmpC$^-$, double porin loss or decreased expression	1	4	4	32

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