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Outbreak of *Klebsiella pneumoniae* Carbapenemase-2-Producing *K. pneumoniae* Sequence Type 11 in Taiwan in 2011

Chun-Ming Lee,[a,b,c] Chun-Hsing Liao,[d] Wen-Sen Lee,[e] Yung-Ching Liu,[f] Jung-Jung Mu,[g] Meng-Chih Lee,[a,h,i] and Po-Ren Hsueh[j]

Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan[a]; Department of Infectious Diseases, Mackay Memorial Hospital, Taipei, Taiwan[b]; Mackay Medicine, Nursing and Management College, Taipei, Taiwan[c]; Department of Internal Medicine, Far Eastern Memorial Hospital, Taipei, Taiwan[d]; Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan[e]; Department of Internal Medicine, Shuang Ho Hospital, Taipei Medical University and School of Medicine, Taipei, Taiwan[f]; Research and Diagnostic Center, Centers for Disease Control, Taipei, Taiwan[g]; Department of Family Medicine, Taichung Hospital, Department of Health, Executive Yuan, Taichung, Taiwan[h]; School of Medicine, Chung Shan Medical University, Taichung, Taiwan[i]; and Departments of Laboratory Medicine and Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan[j]

From June to September 2011, a total of 305 ertapenem-nonsusceptible *Enterobacteriaceae* isolates (MICs of ertapenem ≥ 1 μg/ml) were collected from 11 hospitals in different parts of Taiwan. The MICs of 12 antimicrobial agents against these isolates were determined using the broth microdilution method, and genes for carbapenemases were detected using PCR. Genotypes of isolates possessing carbapenemase genes were identified by pulsed-field gel electrophoresis (PFGE) and multilocus sequence typing. The ertapenem-nonsusceptible *Enterobacteriaceae* isolates included *Klebsiella pneumoniae* ($n = 219$), *Escherichia coli* ($n = 64$), *Enterobacter cloacae* ($n = 15$), and other species ($n = 7$). Seven (2.3%) of the ertapenem-nonsusceptible *Enterobacteriaceae* isolates exhibited colistin MICs of >4 μg/ml, and 24 (7.9%) were not susceptible to tigecycline (MICs > 2 μg/ml). A total of 29 (9.5%) isolates carried genes encoding carbapenemases, namely, *K. pneumoniae* carbapenemase-2 (KPC-2) in 16 (7.3%) isolates of *K. pneumoniae* (KPC-2-KP) and IMP-8 in 5 (2.3%) isolates of *K. pneumoniae*, 5 (33.3%) isolates of *E. cloacae*, 1 isolate of *E. coli*, 1 isolate of *Klebsiella oxytoca*, and one isolate of *Citrobacter freundii*. The 16 KPC-2-KP isolates were isolated from patients at four different hospitals in northern Taiwan. All 16 of the KPC-2-KP isolates were susceptible to amikacin and colistin and had a similar pulsotype (pulsotype 1) and the same sequence type (sequence type 11). Infections due to KPC-2-KP mainly occurred in severely ill patients in the intensive care unit ($n = 14$, 88%). Four patients with infections due to KPC-2-KP died within 14 days of hospitalization. The findings are the first to demonstrate intrahospital and interhospital dissemination of KPC-2-KP in northern Taiwan.

Carbapenems remain the first-line therapy for severe infections caused by extended-spectrum β-lactamase (ESBL)-producing and multidrug-resistant *Enterobacteriaceae* (1, 19, 24, 30). Global surveillance studies have revealed that all carbapenems (ertapenem, imipenem, meropenem, and doripenem) are highly active against these resistant *Enterobacteriaceae* isolates (7, 8, 18). Recently, carbapenem-resistant *Enterobacteriaceae* isolates, particularly *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* (KPC-KP) and New Delhi metallo-β-lactamase-1 (NDM-1)-producing *Enterobacteriaceae* have emerged in many countries as a result of intracontinental and intercontinental spreading (3–6, 20, 23, 25, 27, 31, 32, 34, 35, 38). Carbapenemases, however, are not the only mechanisms associated with resistance to carbapenems. For example, studies have shown that the combination of ESBL-AmpC hyperproduction with porin loss contributes to carbapenem nonsusceptibility (13, 14, 20, 36, 37).

In Taiwan, ESBL production, AmpC β-lactamase overproduction, and decreased outer membrane protein expression combined with an active efflux pump have also been reported to contribute to resistance of *Enterobacteriaceae* to ertapenem (36, 37). KPC-KP- and NDM-1-producing organisms were not reported in Taiwan until 2011, and all of them were imported from China (10, 22).

The purpose of this multicenter surveillance study comprising 11 teaching hospitals located in different parts of Taiwan was to delineate the current status of carbapenem resistance and the molecular basis for the increase in carbapenem resistance among *Enterobacteriaceae* species in Taiwan during the period from June to September 2011.

MATERIALS AND METHODS

Bacterial isolates and hospital settings. From June 2011 to September 2011, a total of 305 nonduplicate isolates of ertapenem-nonsusceptible *Enterobacteriaceae* (MIC values ≥ 1 μg/ml) were collected from 11 hospitals (bed number range, 1,000 to 3,000) located in northern Taiwan (Taipei City and New Taipei City; $n = 7$), central Taiwan (Taichung; $n = 2$), and southern Taiwan (Tainan and Kaohsiung; $n = 2$). The ertapenem-nonsusceptible *Enterobacteriaceae* isolates were obtained from various clinical specimens, namely, sputum ($n = 116$, 38.0%), urine ($n = 95$, 31.1%), wound or pus ($n = 36$, 11.8%), and blood ($n = 35$, 11.5%) and included *Klebsiella pneumoniae* ($n = 219$), *Escherichia coli* ($n = 64$), *Enterobacter cloacae* ($n = 15$), *Enterobacter aerogenes* ($n = 2$), *Serratia marcescens* ($n = 2$), and 1 isolate each of *Klebsiella oxytoca*, *Citrobacter freundii*, and *C. diversus* (see Table S1 in the supplemental material). The isolates

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Address correspondence to Jung-Jung Mu, jjmu@cdc.gov.tw, or Meng-Chih Lee, mcl@csmu.edu.tw.

J.-J.M., M.-C.L., and P.-R.H. contributed equally to this article.

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TABLE 1 MICs of 17 KPC-2-KP isolates to 12 antimicrobial agents and microbiological characteristics of these isolates

Isolate	MIC (μg/ml)[a]												Microbiological characteristics		
	FEP	ATM	ERT	DOR	IMI	MEM	GM	AN	FOS	SXT	CL	TGC	MHT result	Pulsosubtype[b]	ST
A1	>128	>128	>128	32	32	64	0.5	2	>256	0.25	1	0.5	+	PST-2	11
A2	>128	>128	>128	128	64	128	0.5	1	>256	0.25	0.5	0.5	+	PST-5	11
B1	>128	>128	>128	>128	>128	>128	0.5	1	>256	0.25	0.5	0.5	+	PST-2	11
B2	>128	>128	>128	64	32	64	0.5	2	>256	0.25	0.5	1	+	PST-2	11
B3	64	>128	>128	64	64	128	0.5	1	>256	2	0.5	1	+	PST-1	11
B4	128	>128	>128	64	64	128	64	1	128	16	1	1	+	PST-4	11
B5	128	>128	>128	64	32	128	0.5	2	>256	>32	0.5	1	+	PST-2	11
B6	>128	>128	>128	128	32	128	1	2	>256	2	0.5	1	+	PST-2	11
C1	128	>128	>128	32	32	64	0.5	1	64	2	0.5	1	+	PST-1	11
C2	128	>128	>128	64	64	128	0.5	1	256	2	0.5	1	+	PST-1	11
C3	128	>128	>128	64	32	128	0.5	1	128	2	0.5	1	+	PST-1	11
C4	>128	>128	>128	128	64	128	0.25	0.5	64	2	0.5	1	+	PST-6	11
C5	128	>128	>128	64	32	64	0.5	0.5	128	2	0.5	1	+	PST-1	11
C6	128	>128	>128	64	32	64	0.5	0.5	256	2	0.5	1	+	PST-1	11
C7	64	>128	>128	32	16	64	0.5	2	64	2	0.5	2	+	PST-3	11
D1	128	>128	>128	32	32	64	0.5	1	>256	2	1	1	+	PST-1	11
NTUH- 9047 (9)	>128	>128	>128	32	64	64	>128	>128	>256	2	0.5	1	+	PST-1	11

[a] AN, amikacin; ATM, aztreonam; CL, colistin; DOR, doripenem; ERT, ertapenem; ESBL, extended-spectrum β-lactamase production detected by the disk diffusion method (10); FEP, cefepime; FOS, fosfomycin; GM, gentamicin; IMI, imipenem; MEM, meropenem; MHT, modified Hodge test (11); PST, pulsosubtype; ST, sequence type; SXT, trimethoprim-sulfamethoxazole; TGC, tigecycline.

[b] All 17 KPC-KP isolates belonged to PT-1.

were initially identified using a Phoenix PMIC/ID-30 identification system (Becton Dickinson Diagnostic Systems, Sparks, MD) (Table 1).

Antimicrobial susceptibility testing. MIC values were initially determined by the broth microdilution method using the Phoenix PMIC/ID-30 system (Becton Dickinson Diagnostic Systems, Sparks, MD), and the MICs of 12 antimicrobial agents against all isolates that harbored any carbapenemase gene were determined using the agar dilution method according to the guidelines recommended by the Clinical and Laboratory Standards Institute (CLSI) (12). The antimicrobial agents used for susceptibility testing were obtained from their corresponding manufacturers. The concentrations of antimicrobial agents ranged from 0.03 μg/ml to 128 μg/ml. The MIC of each antimicrobial agent was defined as the lowest concentration that inhibited visible growth of the organism. Susceptibility to tigecycline was defined on the basis of the criteria proposed by the U.S. Food and Drug Administration (FDA) (MICs ≤ 2 μg/ml) (16) and the European Committee on Antimicrobial Susceptibility Testing-2011 (EUCAST-2011) (susceptible, MICs ≤ 1 μg/ml) (15).

ESBL-producing isolates were identified using the disk diffusion method as recommended by the CLSI (11). The modified Hodge test was also performed for all isolates harboring carbapenemase genes (11).

Determination of carbapenemase genes. Genes encoding different classes of carbapenemases, including those of class A (KPC, NMC, SME, IMI, and GES), class B (NDM, IMP, VIM, SPM, GIM, and SIM), and class D (OXA-48 and 51-like, 23-like, 24-like, and 58-like enzymes), were identified as previously described (13, 29).

Molecular typing. Genotypes of isolates harboring carbapenemase genes were determined using pulsed-field gel electrophoresis (PFGE) with the restriction enzyme XbaI and multilocus sequence typing (MLST) (http://www.pasteur.fr/recherche/genopole/PF8/mlst/Kpneumoniae.html) (28). Isolates exhibiting PFGE profiles with more than 80% similarity were considered to be closely related strains and defined as being of the same pulsotype (PT). Isolates with the same pulsosubtype (PST) were defined as being closely related strains possessing identical (100% similarity) PFGE profiles. Isolates with the same PST and sequence type (ST) were considered to belong to the same clone. NTUH-9047, the first isolate of KPC-2-producing *K. pneumoniae* (KPC-2-KP) recovered in Taiwan, was also included in this study (9).

Plasmid identification. Plasmid DNA was extracted from isolates of KPC-2 *K. pneumoniae* with a Qiagen midikit (Qiagen, Germantown, MD). HindIII-digested plasmids were separated on a 0.8% agarose gel and transferred to nylon membranes for Southern hybridization. KPC-containing fragments were identified by hybridization with a digoxigenin (Dig)-labeled bla_{KPC}-specific probe (Roche Diagnostics, GmbH, Germany) (13, 29).

RESULTS

Antimicrobial susceptibilities of all ertapenem-nonsusceptible *Enterobacteriaceae* isolates. The MIC ranges, MIC_{50} values, and MIC_{90} values of 20 antimicrobial agents against the 305 ertapenem-nonsusceptible *Enterobacteriaceae* isolates, as well as the rates of susceptibility to said agents, are shown in Table S2 in the supplemental material. Among all ertapenem-nonsusceptible *Enterobacteriaceae* isolates, 69% were susceptible to imipenem, 82% were susceptible to meropenem, and 25% were susceptible to cefepime. The rate of susceptibility to cefepime was higher among *E. coli* (47%) and *E. cloacae* (60%) isolates than among *K. pneumoniae* isolates (16%). The rates of susceptibility to amikacin were 66% for *K. pneumoniae*, 97% for *E. coli*, and 100% for *E. cloacae*. The overall rate of susceptibility to amikacin was 75%. The range of tigecycline MICs was 0.06 μg/ml to 8 μg/ml (MIC_{90} value, 2 μg/ml), and that of colistin was ≤1 μg/ml to >4 μg/ml (MIC_{90} value, ≤1 μg/ml). Seven (2.3%) of the ertapenem-nonsusceptible *Enterobacteriaceae* isolates, including six (2.7%) isolates of *K. pneumoniae* and one (6.7%) isolate of *E. cloacae*, exhibited colistin MIC values of >4 μg/ml. Fifty-five (18.0%) isolates, including 43 (19.6%) *K. pneumonia* isolates, 8 (53.3%) *E. cloacae* isolates, 2 *S. marcescens* isolates, and 1 isolate each of *K. oxytoca* and *E. aerogenes*, were not susceptible to tigecycline on the basis of the criteria (MICs > 1 μg/ml) proposed by EUCAST (15). Twenty-eight isolates (9.2%), including 22 (10.0%) of *K. pneumonia*, 4 (26.7%) of *E. cloacae*, and 2 of *S. marcescens*, were not susceptible to tigecycline (MICs > 2 μg/ml) on the basis of FDA criteria (16). Rates of susceptibility to other agents tested were low.

Genes encoding carbapenemases. Among the 305 ertapenem-

TABLE 2 MICs of 13 isolates possessing genes encoding IMP-8 to 12 antimicrobial agents[a] and their pulsotypes

Isolate no. (hospital)	Bacterium (designation)	ESBL production/ MHT result	MIC (μg/ml)												Pulsotype
			FEP	ATM	ERT	DOR	IMI	MEM	GM	AN	FOS	SXT	CL	TGC	
1 (A)	*K. pneumoniae* (I)	+/+	32	0.5	8	2	2	1	1	2	256	>32	0.5	4	PT-3
2 (A)	*K. pneumoniae* (II)	+/+	16	0.25	4	1	1	0.5	1	2	256	>32	0.5	4	PT-3
3 (A)	*K. pneumoniae* (III)	+/+	16	0.25	4	1	0.5	0.5	1	2	>256	>32	0.5	1	PT-4
4 (H)	*K. pneumoniae* (IV)	+/+	32	16	4	0.5	0.5	0.5	32	1	32	>32	0.5	2	PT-2
5 (H)	*K. pneumoniae* (V)	+/+	32	16	2	0.5	0.5	0.5	32	1	64	>32	0.5	2	PT-2
6 (A)	*E. coli*	+/+	32	64	1	0.12	0.5	0.12	128	2	1	>32	0.5	0.5	NP
7 (K)	*E. cloacae*	NA/+	8	128	1	0.25	0.5	0.25	128	8	8	>32	0.5	1	PT-5
8 (K)	*E. cloacae*	NA/+	8	128	1	0.06	0.25	0.12	128	8	16	>32	0.25	4	PT-6
9 (K)	*E. cloacae*	NA/+	16	>128	4	0.25	0.5	0.25	1	1	32	>32	0.5	4	PT-7
10 (K)	*E. cloacae*	NA/+	2	128	2	0.12	0.25	0.25	1	1	32	>32	0.5	4	PT-7
11 (E)	*E. cloacae*	NA/−	2	128	1	0.06	0.12	0.06	128	8	32	>32	0.25	2	PT-8
12 (A)	*K. oxytoca*	+/−	16	0.25	2	0.5	1	0.5	1	1	16	0.25	0.5	1	NP
13 (E)	*C. freundii*	NA/+	64	128	4	1	2	0.5	128	2	0.5	0.12	0.5	0.5	NP

[a] AN, amikacin; ATM, aztreonam; CL, colistin; DOR, doripenem; ERT, ertapenem; ESBL, extended-spectrum β-lactamase production detected by the disk diffusion method (10); FEP, cefepime; FOS, fosfomycin; GM, gentamicin; IMI, imipenem; MEM, meropenem; MHT, modified Hodge test (11); NA, not available; NP, not performed; SXT, trimethoprim-sulfamethoxazole; TGC, tigecycline.

nonsusceptible *Enterobacteriaceae* isolates, genes for carbapenemases were detected in 29 (9.5%) isolates, namely, 16 (7.3%) isolates of KPC-2-KP and 13 isolates of IMP-8-producing organisms, including 5 (2.3%) isolates of *K. pneumoniae*, 5 (33.3%) isolates of *E. cloacae*, 1 isolate of *E. coli*, 1 isolate of *K. oxytoca*, and 1 isolate of *C. freundii* (Tables 1 and 2).

MICs of 11 antimicrobial agents against carbapenemase-producing ertapenem-nonsusceptible *Enterobacteriaceae*. The MIC ranges of 11 antimicrobial agents against the 16 KPC-2-KP isolates and NTUH-9047, the first isolate of KPC-2 *K. pneumoniae* isolated in Taiwan, were as follows: cefepime, 64 to >128 μg/ml; ertapenem, >128 μg/ml; imipenem, 16 to >128 μg/ml; meropenem, 64 to >128 μg/ml; doripenem, 32 to >128 μg/ml; amikacin, 0.5 to 2 μg/ml; gentamicin, 0.5 to 64 μg/ml (1 isolate with an MIC of 64 mg/liter); sulfamethoxazole-trimethoprim, 0.25 to >32 μg/ml (1 isolate with an MIC of 16 mg/liter and 1 with an MIC of >32 μg/ml); and fosfomycin, 64 to >256 μg/ml (Table 1). The 16 KPC-2-KP isolates were susceptible to colistin (range, 0.5 to 1 μg/ml) and tigecycline (range, 0.5 to 2 μg/ml) (Table 1), and all exhibited positive reactions in the modified Hodge test.

Of the 13 IMP-8-producing ertapenem-nonsusceptible *Enterobacteriaceae* isolates, 2 (1 each of *K. pneumoniae* and *C. freundii*) demonstrated intermediate susceptibility to imipenem, 1 (*K. pneumoniae*) showed intermediate susceptibility to doripenem, and all were susceptible to meropenem (Table 2). Eleven (84.6%) of the isolates were resistant to trimethoprim-sulfamethoxazole (MICs, >32 μg/ml). Tigecycline MICs of 4 μg/ml were found in five (5/14, 38.5%) isolates (two *K. pneumoniae* and three *E. cloacae* isolates). All the five isolates were susceptible to colistin, with MICs of ≤0.5 μg/ml.

Genotypes of KPC-2-KP and IMP-8-producing isolates. The 16 KPC-2-KP and NTUH-9047 isolates were closely related (all belonged to PT-1), had the same sequence type (ST11) (Fig. 1), and were isolated from patients hospitalized at four hospitals in northern Taiwan: hospitals A ($n = 2$), B ($n = 6$), C ($n = 7$), and D ($n = 1$). The distance between hospitals B and C is less than 10 kilometers. Among the 16 KPC-2-KP isolates, six PSTs were identified. Two main PSTs were identified: PST-1 ($n = 8$) in four hospitals (hospital A [NTUH-9047], B [$n = 1$], C [$n = 5$], and D [$n = 1$]) and PST-2 ($n = 5$) in two hospitals (hospitals A [$n = 1$] and B [$n = 4$]). The pulsosubtype (PST-1) of the NTUH-9047 isolate differed from the PSTs (PST-2 and PST-5, respectively) of two subsequently identified KPC-2-KP isolates in hospital A. Similar PTs were also found in four IMP-8-producing *K. pneumoniae* isolates (PT-2 in two isolates from hospital H and PT-3 in two isolates from hospital A) and in two IMP-8-producing *E. cloacae* isolates (PT-6 in two isolates from hospital K) (Fig. 1 and Table 2). A plasmid location of the bla_{KPC-2} gene was found among the six main PSTs of 16 KPC-2-producing *K. pneumoniae* isolates (Fig. 2).

Clinical characteristics of patients with infections due to KPC-2-KP. Demographic and clinical information for the patients with isolations of KPC-2-KP is summarized in Table 3. Patients with KPC-2-KP were found in four different hospitals, and all of them are located in northern Taiwan. The distance between these four hospitals is about 10 kilometers. None of the 16 patients had traveled to China prior to hospitalization, but all had previously received treatment at hospital A, the hospital in which the first case of KPC-2-KP had been isolated (10). Most (14 of 16, 87.5%) of the patients from whom KPC-2-KP was isolated were in intensive care units and were receiving aggressive medical interventions and treatment with multiple antibiotics. Among these 16 patients, 6 had received carbapenems within 2 weeks prior to the isolation of KPC-2-KP. The airway was the most common site of isolation. The duration from admission to KPC-2-KP isolation varied.

DISCUSSION

Our findings in this multicenter, prospective study clearly indicate that there was intrahospital and interhospital dissemination of KPC-2-KP in northern Taiwan and that intrahospital spread of IMP-8-possessing ertapenem-nonsusceptible *Enterobacteriaceae* occurred in several Taiwanese hospitals. We also found that all of the isolates of KPC-2-KP ($n = 16$) had the same pulsotype (PT-1) and the same sequence type (ST11) as the first isolate of KPC-2-KP (NTUH-9047) found in hospital A (10). In addition, the majority of IMP-8 producers were found in ertapenem-nonsusceptible *K. pneumoniae* and *E. cloacae* isolates. The presence of IMP-8 along with ESBL production, AmpC β-lactamase overproduction, and decreased outer membrane protein expression combined with an active efflux pump has been reported to contribute to ertapenem resistance in *E. cloacae* in Taiwan and in other countries (14, 26, 37).

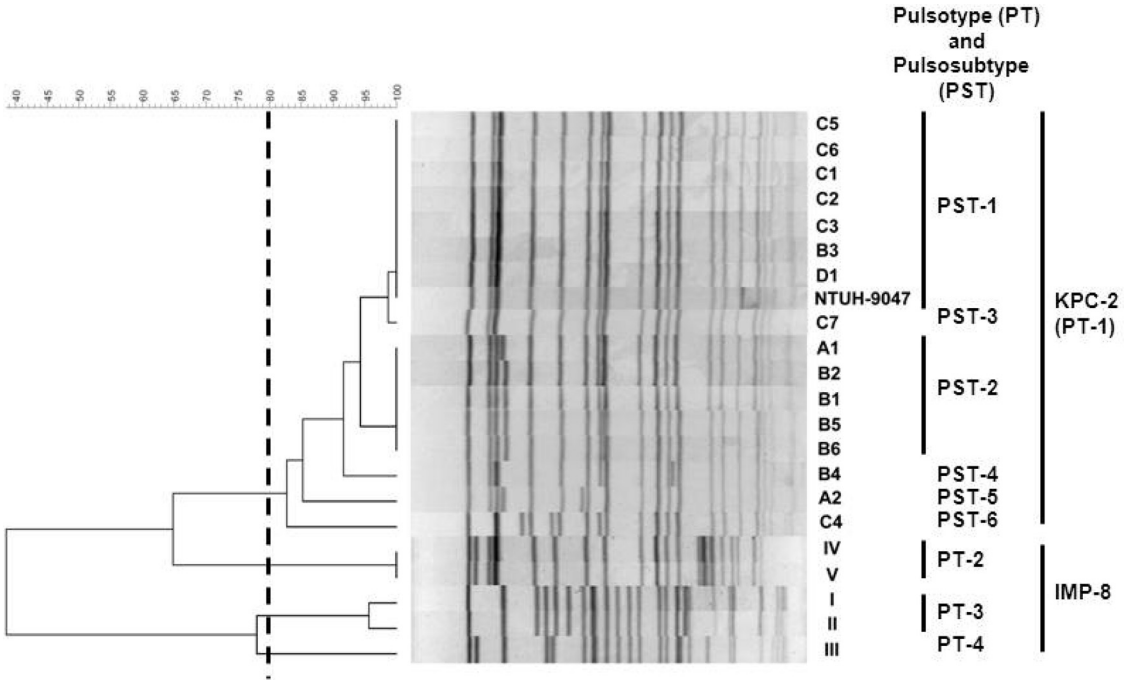

FIG 1 Pulsed-field gel electrophoresis profiles and dendrogram of the 16 KPC-2-KP isolates, 1 KPC-2-KP isolate previously reported (NTUH-9024) (10), and 5 IMP-8-producing *K. pneumoniae* isolates in Taiwan in 2011. See Tables 2 and 3 for isolate designations and the sources of the isolates.

Previous reports demonstrated that the ST11 KPC-KP clone dominated in China and in other Asian countries (2, 29). Interestingly, the endemic clone found in this study shared the same sequence type (29). None of the 16 patients had recently traveled to China; however, because of the close geographic relationship between China and Taiwan and the frequency with which individuals travel between the two countries, the strain associated with this outbreak could have spread from China to Taiwan and could have resided in the community and hospitals without being noticed. In this study, KPC-2-KP was isolated within 3 days of admission in three patients. None of these three patients had recent hospitalization or contact with KPC-2 carriers, suggesting that KPC-2-KP existed not only in the hospitals but also in the community, although the isolation of KPC-2-carrying isolates was not documented in their families or nearby individuals or pets.

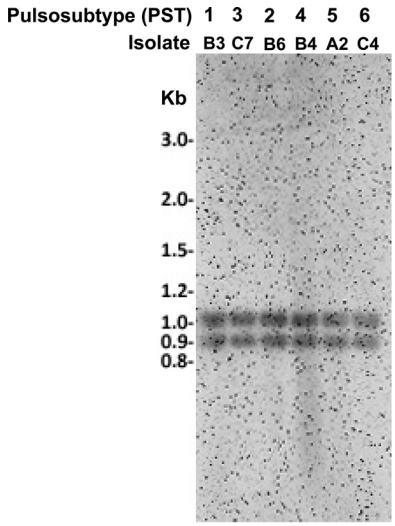

FIG 2 Southern hybridization of plasmids containing KPC fragments obtained from six main PSTs of the 16 KPC-2-producing *K. pneumoniae* isolates.

Inadequate infection control and prior antimicrobial exposure in hospitalized patients, particularly severely ill patients, are the main forces driving the spread of carbapenem-resistant organisms (5, 6, 21, 28). The antimicrobial agents causing selective pressure for KPC-KP include carbapenems, fluoroquinolones, extended-spectrum cephalosporins, β-lactam–β-lactamase inhibitor combinations, and agents with antianaerobe activity (17, 21, 39). Among the 16 patients with infections due to KPC-2-KP, the most common antibiotic administered prior to KPC-KP isolation was piperacillin-tazobactam. In addition, 14 of those patients had received agents with antianaerobe activities, and only 1 had received a carbapenem within 2 weeks prior to the isolation of KPC-2-KP. We speculate that the antianaerobe agents used in these patients might have created a survival niche for *K. pneumoniae* (KPC-KP), a common intestinal bacterium, thereby allowing it to spread from patient to patient and hospital to hospital.

In this study, the 14-day mortality rate among the 16 patients with isolations of KPC-2-KP was 25%, and the in-hospital mortality rate was 62.5%. These findings are similar to those previously reported (17, 21, 28, 33). Gasink et al. reported that KPC-KP infection/colonization was independently associated with in-hospital mortality (17). The effect of KPC-2-KP isolation on the outcomes for these 16 patients is difficult to evaluate because the majority of these patients were severely ill and had multiple comorbidities. The inability to distinguish between colonization and infection (especially the isolates from the airway specimens), the number of coisolates with KPC-2-KP, and the limited activities of antimicrobial agents adminis-

TABLE 3 Demographic and clinical information for patients infected/colonized with KPC-2-KP[a]

Patient (age [yr]/sex)	Hospital/isolate designation	Date (yr/mo/day) of:		Underlying medical condition(s)	ICU related	Site of isolation/type of infection or colonization	Antibiotic regimen within 2 wk:		Mortality	
		Admission	KPC-KP isolation				Prior to KPC-KP isolation	After KPC-2-KP isolation	14 days	In hospital
1 (22/M)	A/A1	2011/6/17	2011/6/20	Becker muscular dystrophy, cardiac arrest after CPR, and ECMO	Yes	Wound/SSI (ECMO related)	Vancomycin, ceftazidime, piperacillin-tazobactam	Piperacillin-tazobactam, tigecycline, colistin	No	No
2 (31/M)	A/A2	2011/6/18	2011/8/21	DM, CKD, ARDS after ECMO	Yes	Sputum/colonization	Vancomycin, cefepime, colistin	Imipenem, colistin, moxifloxacin, vancomycin	No	Yes
3 (81/F)	B/B1	2011/6/14	2011/7/2	Colon cancer stage IV postoperation and chemotherapy, recurrence with bowel obstruction postoperation	Yes	Retroperitoneal abscess	Piperacillin-tazobactam	Doripenem, amikacin	No	Yes
4 (83/F)	B/B2	2011/6/26	2011/7/25	Colon cancer with liver and lung metastasis	Yes	Sputum/colonization	Piperacillin-tazobactam	Imipenem, gentamicin	No	Yes
5 (67/M)	B/B3	2011/7/22	2011/8/9	Subdural hemorrhage postoperation, dementia	Yes	Sputum/colonization	Piperacillin-tazobactam	Piperacillin-tazobactam	No	Np
6 (45/M)	B/B4	2011/8/10	2011/9/5	Cellulitis, acute myeloid leukemia postchemotherapy, neutropenic fever	No	Blood/bacteremia	Vancomycin, cefepime, metronidazole	Colistin, imipenem, amikacin	Yes	Yes
7 (74/F)	B/B5	2011/7/9	2011/9/25	COPD, stroke	Yes	Sputum/colonization	Piperacillin-tazobactam	Piperacillin-tazobactam	No	No
8 (86/F)	B/B6	2011/9/23	2011/10/12	DM, seizure, sick sinus syndrome post-pacemaker installation	Yes	Sputum/colonization	Piperacillin-tazobactam	Levofloxacin, trimethoprim-sulfamethoxazole	No	No
9 (81/M)	C/C1	2011/5/17	2011/6/8	DM, CAD, post-coronary artery bypass graft	Yes	Sputum	Piperacillin-tazobactam, amikacin	Amikacin	Yes	Yes
10 (84/M)	C/C2	2011/6/17	2011/7/2	DM, dissection of aorta	Yes	Sputum/colonization	Cefmetazole, cefepime, metronidazole	No	Yes	Yes
11 (57/F)	C/C3	2011/5/1	2011/6/22	DM, CAD, post-coronary artery bypass graft	Yes	Wound/SSI	Piperacillin-tazobactam, meropenem	Meropenem	No	Yes
12 (84/F)	C/C4	2011/6/21	2011/6/24	Pneumonia with respiratory failure	Yes	Urine/colonization	Ceftriaxone, sulbactam	Cefmetazole, amikacin	No	Yes
13 (78/M)	C/C5	2011/6/28	2011/7/6	Parkinson's disease, pneumonia with respiratory failure	Yes	Sputum/VAP	Piperacillin-tazobactam	Piperacillin-tazobactam, amikacin	No	No
14 (89/M)	C/C6	2011/8/1	2011/8/1	Pneumonia with septic shock	No	Sputum/VAP	Cefazolin	Imipenem	Yes	Yes
15 (77/M)	C/C7	2011/7/28	2011/8/29	Pressure sore, septic shock, UTI	Yes	Urine/UTI	Piperacillin-tazobactam, daptomycin	Doripenem	No	No
16 (90/M)	D/D1	2011/8/2	2011/8/15	CKD, urothelial carcinoma with lung and brain metastasis	Yes	Sputum/colonization	Cefazolin, cefoperazone-sulbactam	No	No	Yes

[a] ARDS, acute respiratory distress syndrome; CAD, coronary arterial disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; DM, diabetes mellitus; ECMO, extracorporeal membrane oxygenation; F, female; ICU, intensive care unit; M, male; SSI, surgical site infection; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.

tered all contributed to the outcomes for these patients (17, 28). Furthermore, based on the MIC values of antibiotics against this epidemic strain, tigecycline, colistin, and aminoglycosides should have been effective for the treatment of infections caused by this organism (39). However, among the eight patients who received the above-mentioned agents, the in-hospital mortality rate was 75%. The one patient with KPC-2-KP bacteremia died in spite of concomitant colistin and amikacin treatment.

In conclusion, in this multicenter surveillance study, we identified the first outbreak of intrahospital and interhospital dissemination of KPC-2-KP in northern Taiwan. Although only four hospitals from central and southern Taiwan were included in this study, the fact that no KPC-bearing isolates were identified in these regions does not mean that these regions must be clear of KPC-bearing isolates. Further nationwide surveillance of KPC-KP is necessary, and strict infection control measures should be enforced.

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