



PERSPECTIVES

Nationwide spread of *Klebsiella pneumoniae* carbapenemase-2-producing *K. pneumoniae* sequence type 11 in Taiwan



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Since the past decade, carbapenem-resistant Enterobacteriaceae isolates, particularly *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* and New Delhi metallo- β -lactamase-1 (NDM-1)-producing Enterobacteriaceae, have emerged in health care settings of many countries.^{1,2} Apart from NDM, which is endemic in the Indian subcontinent, KPC was first reported among *K. pneumoniae* in the United States in 2001³ and has also been proven to possess great potential for intra- and interhospital dissemination worldwide. The first clinical KPC-producing *K. pneumoniae* isolate in Taiwan was obtained in 2010 from a patient with bacteremia who had just returned from Zhejiang Province, the epicenter of the KPC-2 endemic in China.⁴ For most clinical laboratories, however, it is difficult to judge the existence of carbapenemases in Enterobacteriaceae through minimum inhibitory concentration (MIC) levels against carbapenem agents alone.

In 2009, by means of the modified Hodge test, no ertapenem-nonsusceptible (NS; MIC > 0.25 μ g/mL) Enterobacteriaceae isolates of class A carbapenemase production

were detected in intensive care units in Taiwan.⁵ However, using the MIC breakpoints recommended by the Clinical and Laboratory Standards Institute (CLSI) in 2011, we found alarmingly high rates of nonsusceptibility of *Enterobacter cloacae* and *K. pneumoniae* to ertapenem (40.5% and 24.5%, respectively).⁵ Subsequently, using the polymerase chain reaction method and electrophoresis analysis, two nationwide surveys in Taiwan investigated the 2011 prevalence rates of Enterobacteriaceae carriers of carbapenemases (class A, class B)⁶ and elucidated the main resistance mechanisms of carbapenem-NS Enterobacteriaceae isolates collected in 2010 and 2012,⁷ respectively. The first survey, undertaken by Lee et al.,⁶ revealed that 5.2% (16 isolates) of ertapenem-NS (MIC > 0.5 μ g/mL, by CLSI 2012 standards) Enterobacteriaceae isolates (all were *K. pneumoniae*) in 2011 harbored genes encoding KPC-2 carbapenemase. Additionally, a similar pulsotype and the same sequence type (ST) 11 ($n = 16$) were found among all KPC-2-producing *K. pneumoniae* isolates in hospitals located in northern Taiwan. The second survey, conducted by Chiu et al.,⁷ revealed that the prevalence rate of resistant isolates (imipenem or meropenem MIC > 1.0 μ g/mL, by CLSI 2012 standards) harboring various carbapenemase genes (primarily *bla*_{KPC-2}) was significantly higher in 2012 than in 2010 [22.3% (55 isolates) vs. 6.0% (6 isolates) for overall

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carbapenemases, $p = 0.0003$; 16.6% (41 isolates) vs. 0% for prevalence of KPC-2 carrier among *K. pneumoniae*, $p < 0.0001$; both were analyzed with the Chi-square test]. Apart from carbapenemases, other factors governing resistance comprised deficiency of outer membrane protein (Omp, especially OmpK35) and production of AmpC enzyme (mostly DHA-1 subtype) as well as extended-spectrum β -lactamase (ESBL, primarily *bla*_{CTX-M}, followed by *bla*_{SHV}). The combination of these factors likely conferred medium-to-high resistance to carbapenem agents (especially to ertapenem, imipenem). Thus, in Taiwan, factors other than carbapenemases still account for the major *in vitro* resistance mechanisms responsible for carbapenem non-susceptibility. In addition, typing analysis of the multilocus sequence type revealed that the ST 11 *K. pneumoniae* strain was the predominant KPC clone throughout Taiwan in 2012. These facts strongly suggest that occult interhospital spread of KPC-*K. pneumoniae* in Taiwan probably emerged in 2011.

Data on ertapenem-NS (MIC > 0.5 $\mu\text{g}/\text{mL}$) Enterobacteriaceae in Taiwan differ markedly from the data obtained from the countries in the Asia Pacific region (2008–2009)⁸ targeting at intra-abdominal Enterobacteriaceae isolates. In that large-scale survey,⁸ 11.0% (77 isolates) of resistant isolates had genes encoding carbapenemases (primarily *bla*_{NDM-1}, followed by *bla*_{IMP} and *bla*_{OXA}) and had different AmpC enzymes (dominated by *bla*_{CMY-2}). The percentages of KPC-2 (class A) and class B β -lactamases among all carbapenem-NS Enterobacteriaceae isolates collected from 2010 through 2012^{6,7} in Taiwan are illustrated in Fig. 1.

Two surveys^{5,9} focusing on ertapenem-NS (MIC > 0.25 $\mu\text{g}/\text{mL}$) Enterobacteriaceae isolates without KPC production in Taiwan provided important *in vitro* susceptibility information on β -lactam agents. Cheng et al.⁹ found that regardless of ESBL production, a significant portion of ertapenem-NS isolates (45.8% of *Escherichia coli*, 53% of *K. pneumoniae*, and 86.1% of *Enterobacter cloacae* isolates) was *in vitro* susceptible to cefepime according to CLSI 2011 standards (i.e., MIC level ≤ 8 $\mu\text{g}/\text{mL}$). However, the production of

ESBL enzyme lowered the susceptibility rates to cefepime to a large extent.⁹ In addition, with respect to the ertapenem-NS Enterobacteriaceae isolates (consisting of *E. coli*, *K. pneumoniae*, and *E. cloacae*) without class A carbapenemase, Jean et al.⁵ noted that carbapenem non-susceptibility concordance (between ertapenem and imipenem, meropenem, doripenem) emerges once ertapenem MIC values are ≥ 4 $\mu\text{g}/\text{mL}$. This finding indicates that we likely could prescribe any of the other three carbapenem agents to treat infections caused by ertapenem-NS (MICs ranging from 0.5 to 2 $\mu\text{g}/\text{mL}$) Enterobacteriaceae without KPC production. The clinical application of these valuable *in vitro* susceptibility data, however, requires evaluation by well-designed clinical trials.

In comparison to β -lactam agents, tigecycline and colistin grossly showed low (<20%) *in vitro* nonsusceptible rates against carbapenem-NS Enterobacteriaceae isolates during the period 2010–2012 in Taiwan.^{6,7} Furthermore, the activity of colistin against KPC-2-producing isolates appears to be similar to that of tigecycline with regard to *in vitro* susceptibility, despite the fact that the activity of tigecycline was assessed with the criteria proposed by the U.S. Food and Drug Administration (≤ 2 $\mu\text{g}/\text{mL}$; defined as susceptible category).⁶ Nevertheless, the international spread of genetic elements encoding KPC is still a worrisome concern because of the escalating trend toward nonsusceptibility to these two novel agents after clinical use,^{10,11} and because infections due to KPC are associated with a high case fatality rate.¹²

Currently, there is no specific infection control strategy for carbapenem-NS Enterobacteriaceae. We think that therapy comprising multiple antibiotics as well as contact isolation are appropriate measures for dealing with infections caused by pandrug-resistant KPC-producing Enterobacteriaceae isolates in clinical settings. Periodic targeted surveillance and development of new effective antimicrobial drugs are urgently needed.

Conflicts of interest

All authors report no conflicts of interest relevant to this article.

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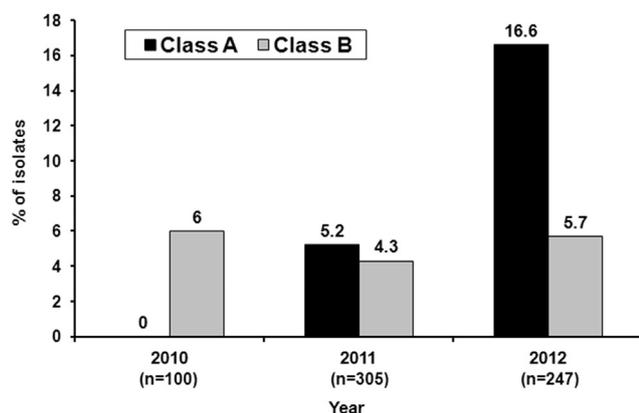


Figure 1. Percentages of Ambler class A (all were *bla*_{KPC-2}) and class B β -lactamases (including *bla*_{IMP-8}, *bla*_{NDM-1}, and *bla*_{VIM-1}) among carbapenem-nonsusceptible Enterobacteriaceae isolates collected from hospitals throughout Taiwan, during the period 2010–2012.

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