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Novel KPC Variant from a Carbapenem-Resistant Strain of *Klebsiella pneumoniae* in a Chinese Hospital

To the Editor—Klebsiella pneumoniae carbapenemase (KPC) was first reported to be the carbapenem-hydrolyzing β-lactamase from a carbapenem-resistant strain of *K. pneumoniae* in 1996[1] and was termed KPC-1. Two years later, KPC-2 was discovered by the same group.[2] However, a bla_{KPC-1} sequence error was found, and the bla_{KPC-1} and bla_{KPC-2} sequences were confirmed as identical soon afterward.[1] To date, 9 other variants (KPC-3 to KPC-11) have been reported (http://www.lahey.org/studies). Among all of these carbapenemases, KPC-2, which had been discovered in many areas, was the predominant one and played a crucial role in carbapenem resistance of *K. pneumoniae*. We isolated a strain of *K. pneumoniae* carrying a novel KPC variant from an inpatient in the First Affiliated Hospital, College of Medicine, Zhejiang University, in the Hangzhou city of China.

An 81-year-old man with acute exacerbation of chronic obstructive pulmonary disease accompanied by gastrointestinal hemorrhage was admitted to our hospital on February 27, 2010. An exploratory laparotomy was performed on March 20, and colorectal polyps were found and removed. Three days later, abdominal drainage appeared, and a strain of *K. pneumoniae*, labeled zjm002, was isolated from the drainage fluid.

The isolate was identified by Vitek gram-negative identification cards (bioMérieux). Antimicrobial susceptibility tests of 9 antibiotics were performed by the microdilution method with cation-adjusted Mueller–Hinton broth (Oxoid) according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI). The minimum inhibitory concentrations of 26 other antibiotics were determined by the Etest technique (bioMérieux) according to the manufacturer's instructions. The susceptibility breakpoints were interpreted as recommended by the CLSI and previous reports. The strain zjm002 was sensitive to amikacin, tigecycline, chloramphenicol, and trimethoprim-sulfamethoxazole and intermediate sensitive to tetracycline, but it was resistant to all other 27 antibiotics (Table 1).

A modified Hodge test (MHT), which might assist in confirming the presence of carbapenemase, was carried out according to Endimiani et al.[3] As a result, the positivity of MHT for this isolate indicated that it carried carbapenemase. Since MHT could not exclusively detect the KPC-type carbapenemase, we detected bla_{KPC} and an additional 39 β-lactamases genes, including 13 class A carbapenemases genes (bla_{TEM}, bla_{SHV}, bla_{CTX-M1}, bla_{CTX-M2}, bla_{CTX-M8}, bla_{CTX-M9}, $bla_{CTX-M25}$, bla_{PER}, bla_{VEB}, bla_{GES}, bla_{CARB}, bla_{RTG}, bla_{LAP}), 10 class B carbapenemases genes (bla_{IMP}, bla_{VIM}, bla_{SIM}, bla_{SPM}, bla_{GIM}, bla_{AIM}, bla_{NDM}, bla_{KHM}, bla_{TMB}, bla_{DIM}), 8 class C carbapenemases genes (bla_{LEN}, bla_{OKP}, bla_{DHA}, $bla_{ACT/MIR}$, $bla_{LAT/CMY}$, $bla_{MOX/CMY}$, bla_{FOX}, bla_{ACC}), and 8 class D carbapenemases genes (bla_{OXA-1}, bla_{OXA-2}, bla_{OXA-10}, bla_{OXA-23}, bla_{OXA-24}, bla_{OXA-48}, bla_{OXA-51}, bla_{OXA-58}). Primer pairs for bla_{KPC} and bla_{TEM} polymerase chain reaction detection were 5′-ATGTCACTGTATCGCCGTCTA-3′ and 5′-TTACTGCCCGTTGACGCCCAA-3′ for bla_{KPC} and 5′-AGGAAGAGTATGATTCAACA-3′ and 5′-CTCGTCGTTTGGTATGGC-3′ for bla_{TEM}. The amplicons were sequenced on an ABI PRISM3730 sequencer analyzer (Applied Biosystems). As a result, bla_{KPC} and bla_{TEM} were detected, whereas the remaining 38 genes were not. The presence of bla_{TEM}, confirmed as bla_{TEM-1}, was determinated by sequencing and Blast analysis. The amino acid sequence of KPC showed an amino acid change

TABLE 1. Antimicrobial Susceptibilities of the Clinical Isolate Labeled zjm002

Antimicrobial agent	Etest	Agar dilution	Clinical laboratory report
Ampicillin	≥256		R
Ampicillin/sulbactam	≥256		R
Amoxicillin/clavulanic acid	≥256		R
Cefalotin	≥256		R
Cefoxitin	≥256		R
Cefuroxime	≥256		R
Ceftazidime	≥256		R
Ceftriaxone	≥256		R
Cefotaxime	≥256		R
Cefepime	≥256		R
Aztreonam	≥256		R
Imipenem	≥32		R
Meropenem	≥32		R
Amikacin	12		S
Tobramycin	16		R
Netilmicin	32		R
Norfloxacin	≥32		R
Ofloxacin	≥32		R
Ciprofloxacin	≥32		R
Levofloxacin	≥32		R
Tetracycline	8		I
Tigecycline	1.5		S
Chloramphenicol	6		S
Trimethoprim-sulfamethoxazole	1.5		S
Ticarcillin/clavulanic acid	≥256		R
Cefoperazone/sulbactam	≥256		R
Piperacillin,		≥128	R
Piperacillin/tazobactam		≥4	R
Cefoperazone		≥64	R
Cefotetan		≥64	R
Ertapenem		≥8	R
Gentamycin		2	S
Polymyxin E		0.5	S
Polymyxin B		0.5	S
Fosfomycin		≥256	R

NOTE. I, intermediate sensitive; R, resistant; S, sensitive.

(Leu(168)→Met) when compared with the sequence of KPC-2, so this carbapenemase was confirmed to be a novel variant designated KPC-2-like (GenBank accession no. HQ258934).

As an important subgroup of class A carbapenemases, KPC has spread among Enterobacteriaceae throughout the world.[4] The bla_{KPC} gene is often located on a Tn*3*-like transposon, Tn*4401*, which might mediate the rapid gene spread. Tn*4401* was inserted on different-sized plasmids that belonged to different incompatibility groups.[5]

Though KPC played a major role in high-level resistance to carbapenems and other β-lactams, several other β-lactamases, such as TEM, SHV, and CTX-M enzymes, also might have existed in *K. pneumoniae* simultaneously.[6,7] However, in our study, only bla_{TEM} and bla_{KPC} were discovered in zjm002. Considering that the TEM enzyme contributed nothing directly to carbapenem resistance, the KPC enzyme might be the result of it.

There were some other mechanisms, for instance, alterations in the outer membrane proteins of OmpK35/OmpK36 and overexpressions of efflux pumps, involving high levels of resistance to carbapenems.[7] To zjm002, these mechanisms were unclear.

So far, 11 types of KPC enzymes were discovered all over the world. KPC-3 was found to differ from KPC-2 by a single amino acid substitution (His(272)→Tyr).[8] Similarly, compared with KPC-2, in KPC-5 there was a single amino acid substitution[9] (KPC-6 [EU555534], KPC-11 [HM066995]). Furthermore, two amino acid substitutions were found in KPC-4[5] (KPC-7 [EU729727], KPC-8 [FJ234412], KPC-9 [FJ624872], KPC-10 [GQ140348]), compared with KPC-2. Our research confirmed that the KPC enzyme carried by zjm002 was a novel variant. As this variant shared 99% homology with KPC-2 from Genbank, it was termed KPC-2-like carbapenemases.

In clinic, owing to the carbapenem resistance and sensitiveness to 2 aminoglycosides (amikacin and gentamycin), carbapenems and other β-lactams were abdicated, and etimicin, a type of aminoglycoside, was utilized to control the abdominal infection. To our great relief, 6 days later, the therapy was successful in clearing the abdominal drainage.

Accompanied by the dissemination of KPC-2 throughout the world, novel KPC variants emerged continuously. In our study, a novel KPC variant termed KPC-2-like was discovered in a *K. pneumoniae* isolate from the abdominal drainage of an 81-year-old patient. This KPC-2-like carbapenemase shared 99% homology with KPC-2. However, an attempt to transfer carbapenem resistance or to present the biochemical characterization of this new variant should be further performed. All β-lactams including carbapenems were virtually useless; etimicin was chosen so that the abdominal infection was controlled. KPC carbapenemases posed serious challenges to clinical therapy and the health of patients. Surveillance of the spread of KPC-producing *K. pneumoniae* should be urgently undertaken.

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Investigation and Control of a Nosocomial Norovirus Outbreak in a Long-Term Care Facility

To the Editor—We report the investigation and control of an important nosocomial outbreak of norovirus infections that occurred in a long-term care facility (240 beds on 3 floors) affiliated with the university hospital of Brest, France, during the winter of 2008.

Norovirus is an RNA virus of the *Caliciviridae* family and the agent that causes most nonbacterial gastroenteritis.[1] Transmission is essentially fecal-oral, either direct through

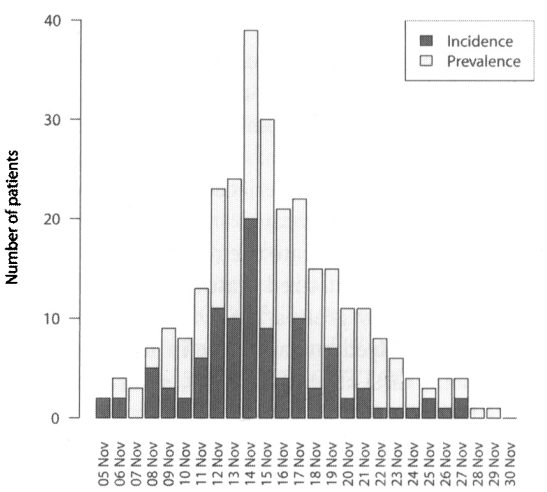

FIGURE 1. Winter 2008 norovirus outbreak in René Fortin long-term care facility: incident and prevalent cases, as daily observed.