Sir,

The emergence and dissemination of Klebsiella pneumoniae strains harbouring carbapenemases is a serious concern. Klebsiella pneumoniae carbapenemase (KPC) enzymes belong to molecular class A and are able to hydrolyse most β-lactams including carbapenems. Since the initial report of a KPC β-lactamase from a strain of K. pneumoniae in 1996, KPC producers have been reported from various geographical regions. Current reports indicate that KPC-producing isolates are widespread in China, Israel, Greece, South America and the USA, where the epidemiology of KPC in the hospital setting is changing. Fortunately, these strains are still rare in western and northern Europe, but their detection remains difficult.

Since 2003, patients hospitalized in the surgical ward of our hospital have been systematically screened on admission and weekly thereafter for intestinal carriage of bacteria producing extended-spectrum β-lactamases (ESBLs) and carbapenemases by plating rectal swabs on Drigalski agar containing 0.5 mg/L cefotaxime and MacConkey agar containing 2 mg/L ceftazidime (AES Laboratoire, Combourg, France). We report here four patients with K. pneumoniae producing KPC-2 and SHV-12. The first case was a patient transferred in July 2009 from Crete for treatment of recurrent angiocholitis on a biliary stent. The patient was negative on the day of admission, but 3 days later a further stool sample grew with ESBL-producing K. pneumoniae. This first isolate was not suspected to produce a carbapenemase since testing for susceptibility to imipenem using a disc diffusion method showed a diameter of 24 mm and an MIC of 1.5 mg/L by Etest (Bio-Rad, Marne la Coquette, France), both considered as susceptible according to the national recommendations of the Antiobigram Committee of the French Society for Microbiology. However, in September, KPC-producing K. pneumoniae were isolated from three further patients (two from biliary fluid and one from tracheal fluid) hospitalized in the same ward at the same time. As KPC-producing K. pneumoniae are exceptional in France and described only in patients transferred from abroad (particularly Greece and Israel), it was decided to re-investigate all ESBL-producing K. pneumoniae isolates over the previous 6 months and to screen for carbapenemase production using the modified Hodge test and PCR. The only strain that was also positive for blkpnc and which matched the three known KPC-positive isolates was the one isolated in July from the patient from Crete, who was thus potentially the index case. An epidemiological study (data not shown) revealed opportunities for cross-transmission to have occurred between the four patients.

This outbreak underlines the difficulty of identifying KPC-mediated carbapenem resistance using routine methods. The K. pneumoniae isolates from the latter three patients showed reduced susceptibility to imipenem, with a diameter of 21 mm, considered to indicate an intermediate level of resistance, an MIC of 2 mg/L and small colonies growing inside the zone of inhibition. All isolates, including the strain recovered from the Greek patient, exhibited resistance to other antibiotics tested: fluoroquinolones, tobramycin, amikacin and co-trimoxazole. The isolates were only susceptible to colistin and gentamicin. Using the modified Hodge test and EDTA-disc synergy, all isolates were phenotypically positive for carbapenemase production, but negative for metallo-β-lactamase (MBL) production. ESBL screening tests using the double disc diffusion test between clavulanic acid and third-generation cephalosporins showed a synergy between ceftazidime or cefepime and clavulanic acid.

References


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Outbreak of Klebsiella pneumoniae producing KPC-2 and SHV-12 in a French hospital

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Enterobacterial repetitive intergenic consensus-PCR (ERIC-PCR) analysis of 10 isolates including the isolate from the first case and 9 isolates recovered from the other 3 patients (1 rectal swab and 2 clinical isolates from each of the 3 patients) showed the same profile compared with 2 non-epidemiologically related KPC K. pneumoniae producers isolated from Israel (data not shown).

The detection of β-lactamase genes was performed by a multiplex PCR using a panel of primers specific for the detection of KPC, acquired AmpCs, OXA, MBL and ESBLs. PCR products were sequenced on both strands. All isolates contained genes for blaKPC-2, blaSHV-12, blaTEM-1 and blaOXA-9. Multi locus sequence typing, performed as previously described, showed that all strains belong to sequence type (ST) 258, which is emerging worldwide. 

Escherichia coli DH10B was successfully transformed by electroporation with a plasmid encoding both KPC and SHV-12. Plasmid analysis experiments showed three plasmids in the parental strains (p1 > 130 kb, 20 kb < p2 < 54 kb and p3 < 20 kb), whereas electroporants showed only the p2 plasmid carrying both blaKPC-2 and blaSHV-12. These two genes, blaKPC-2 and blaSHV-12, have already been reported either in the same plasmid or in different plasmids. According to the PCR replicon typing described by Carratoli et al., plasmid carrying blaKPC-2-carrying plasmid was negative for all replicons in the electroporants.

The epidemic spread of carbapenemase-producing strains from colonized patients transferred from Greece is now well documented and should be taken seriously. The potential of KPC producers to disseminate, together with the difficulties in their detection, highlights the need for accurate screening methods for these enzymes and the importance of implementing early drastic hygiene measures to limit the size and duration of outbreaks. Because our surgical centre specializes in biliary diseases and liver transplantation, among patients from foreign countries, 28/87 and 27/82 came from areas where KPC are frequent, respectively, in 2008 and 2009. The development of international medicine suggests that pre-emptive isolation of patients at risk of carrying multidrug-resistant strains, such as those transferred from centres where outbreaks are ongoing, can help to prevent spread. Currently, screening for carbapenemase-producing strains for patients coming from abroad is recommended at Assistance Publique-Hôpitaux de Paris (AP-HP), the largest public hospital institution in France (38 hospitals, 23000 beds) to which our hospital belongs.

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Differential β-lactam resistance response driven by ampD or dacB (PBP4) inactivation in genetically diverse Pseudomonas aeruginosa strains

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