emergence of highly diffusible ESBL gene-carrying IncI1 plasmids in these strains is of concern, and further surveillance of this genotype is warranted, both in humans and animals.

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References

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Transfer of OXA-48-positive carbapenem-resistant Klebsiella pneumoniae from Turkey to France

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Sir,

Carbapenemases possess the most consistent in vitro activity against expanded-spectrum β-lactamase (ESBL)-producing Klebsiella pneumoniae. Resistance to carbapenem, while still rare in Enterobacteriaceae, is increasing and represents a significant threat for the management of multidrug-resistant isolates.1 In Enterobacteriaceae, this resistance can be mediated by class A β-lactamases (IMP, VIM and NDM), plasmid-mediated clavulanic acid-inhibited β-lactamases (NmcA, IMI, SME, GES and KPC) and the class D β-lactamase OXA-48.2 The OXA-48 enzyme, initially identified from a carbapenem-resistant K. pneumoniae isolate from Istanbul, Turkey, hydrolyses penicillins, cephalosporins and imipenem, but spares expanded-spectrum cephalosporins.3 Outbreaks of OXA-48-producing K. pneumoniae and of other enterobacterial isolates have been described in several cities in Turkey.3 Subsequently, single isolates of OXA-48-type-producing K. pneumoniae have been reported from Belgium, the UK, Israel, Morocco, Lebanon and Tunisia.4 We describe here a nosocomial spread of carbapenem-resistant K. pneumoniae strains expressing OXA-48 in a French hospital after a transfer from Turkey.

In late 2010, a pregnant woman was admitted for premature rupture of choriomnionic membranes and fever at the hospital of Chambéry, south-east France. She was treated successively with amoxicillin, metronidazole and netilmicin, then with amoxicillin/clavulanic acid, and finally with cefixime. She had returned from Kayseri, Turkey, where she had consulted for her pregnancy follow-up at a hospital, but was not hospitalized. There, she
received a treatment with cefuroxime (unknown dose and treatment duration) for suspicion of a urinary tract infection. In France, she gave birth to a premature infant who died several hours later of sepsis associated with hyaline membrane disease, despite an antibiotic treatment comprising amikacin and cefotaxime. The mother was treated for endometritis for 3 weeks with ceftriaxone and had a favourable outcome. Cultures of placenta and neonatal samples (ear, gastric fluid, central catheter and blood) grew K. pneumoniae isolates. Antibiotic susceptibilities were first determined using the Vitek 2 system (bioMérieux, Marcy l’Etoile, France) (software 04.02), reporting resistance to carbapenems for these isolates. Additionally, the MICs of several antibiotics were determined using Etest strips (AB bioMérieux, Solna, Sweden). The isolates were resistant to penicillins, including amoxicillin, ticarcillin, amoxicillin/clavulanic acid, piperacillin and piperacillin/tazobactam. Also, the isolates had heterogeneous decreased susceptibility to carbapenems, with MICs of ertapenem, imipenem, meropenem and doripenem being 1, 0.5, 0.5 and 0.25 mg/L, respectively; thus, still in the susceptibility range according to the CLSI guidelines updated in June 2010 (except for ertapenem). They were susceptible to expanded-spectrum cephalosporins (MICs of ceftazidime and cefotaxime being 0.25 and 1 mg/L, respectively), aminoglycosides, fluoroquinolones and co-trimoxazole. Specific primers were used for PCR detection of carbapenemase genes for all isolates and the blaOXA-48 gene was identified. Additional screening of β-lactamase-encoding genes, based on those that have been previously identified in OXA-48-positive K. pneumoniae isolates, identified the blaTEM-1 gene in addition to the intrinsic blaSHV gene.

To comply with the French guidelines for the prevention of spread of multidrug-resistant Gram-negative isolates, the patient was placed in isolation and a rectal swab screening was performed for all patients (infants and mothers) hospitalized in the same unit once a week during the following 3 weeks. The chromogen CPS culture medium (bioMérieux, La Balme-les-Grottes, France) was used for that purpose, and colonies potentially corresponding to a K. pneumoniae strain were tested for antibiotic susceptibility. In total, 21 mothers were screened, together with 13 infants. Fourteen days after implementation of this screening, a neonate was identified as a carrier of a K. pneumoniae isolate that exhibited a similar pattern of resistance to that of the previous OXA-48-positive isolate. This newborn developed pneumonia, which was also associated with a K. pneumoniae isolate (pharyngeal aspiration). He was treated empirically with amoxicillin and amikacin that was further switched to cefotaxime and amikacin, with a favourable outcome. Both K. pneumoniae isolates had the exact same resistance phenotype as described above. The follow-up of the rectal screening indicated that the newborn was still positive for this K. pneumoniae isolate 1 month after its initial identification (ongoing survey).

The genetic relationship between the different isolates studied by PFGE revealed that the two OXA-48-producing isolates were clonally related. However, they were different from the two main OXA-48-positive K. pneumoniae clones previously identified in Istanbul (data not shown). Plasmid DNA extraction according to the Kieser technique showed that these isolates had a blaOXA-48 gene carried on a self-conjugative 70 kb plasmid. Using specific primers as described previously, we identified the repP gene that is considered as a marker gene for the blaOXA-48 plasmid scaffold. Therefore, the plasmid content of the OXA-48-producing K. pneumoniae clone identified here was identical to that previously reported for other OXA-48 K. pneumoniae of diverse geographical origin. Also, PCR mapping identified the Tn1999.2 transposon previously identified in Turkish isolates.

The present study provides several interesting pieces of information. It underlines that laboratory detection of OXA-48 producers may be difficult when only decreased susceptibility to carbapenems is observed, together with a susceptibility to expanded-spectrum cephalosporins. The development of this nosocomial outbreak following an initial importation through a patient that had been hospitalized in a foreign hospital justifies the screening for multidrug-resistant bacteria (in particular carbapenemase producers) at admission. However, since the OXA-48 strain was susceptible both to carbapenems and expanded-spectrum cephalosporins, none of the currently recommended screening media for carbapenemase producers could be safely used for this detection (CHROMagar, CHROMagar Ltd Paris, and ChromID ESBL, bioMérieux). Therefore, there is a need for a screening medium for those carbapenemase producers. The OXA-48 producers corresponded to a previously unidentified clone that, however, harboured a known 70 kb blaOXA-48-positive plasmid, further emphasizing the important role of that plasmid as the vector of spread of this resistance determinant.

Interestingly, the potential therapeutic effect of expanded-spectrum cephalosporins shall be further evaluated for treating infections due to OXA-48 producers (when not co-producing an ESBL), since OXA-48 itself does not significantly hydrolyse expanded-spectrum cephalosporins and a cephalosporin-containing treatment was efficient here.

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**Transparency declarations**

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