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KPC-producing *Klebsiella pneumoniae*, finally targeting Turkey

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Abstract

We report here the first identification of the worldwide spread of *Klebsiella pneumoniae* carbapenemase-2-producing and carbapenem-resistant *K. pneumoniae* clone ST258 in Turkey, a country where the distantly-related carbapenemase OXA-48 is known to be endemic. Worryingly, this isolate was also resistant to colistin, now considered to be the last-resort antibiotic for carbapenem-resistant isolates.

Keywords: Carbapenemase, colistin, *Klebsiella pneumoniae*, *Klebsiella pneumoniae* carbapenemase, ST258
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Carbapenem-resistant enterobacterial isolates, currently spreading worldwide, are of major public health concern in both developed and developing countries [1]. Among the most commonly identified carbapenemases identified in Enterobacteriaceae, are the *Klebsiella pneumoniae* carbapenemases (KPC) [1].

We report here on an 80-year-old female patient transferred from a Romanian hospital and admitted in November 2012 to the Intensive Care Unit of a hospital located close to Istanbul, Turkey. Upon admission she presented severe nosocomial pneumonia. Sputum culture grew *Acinetobacter baumannii*, and a rectal swab taken for screening purposes grew an extended-spectrum β-lactamase-producing *K. pneumoniae*. The patient was treated with meropenem for 14 days and a carbapenem-resistant *K. pneumoniae* (isolate A) was isolated from an endotracheal aspirate culture 21 days after her admission. Colistin was added to the meropenem and, after 10 days, endotracheal aspirate cultures remained negative and the antibiotic regimen was discontinued. Four days after the antibiotherapy was stopped, a carbapenem-resistant and colistin-resistant *K. pneumoniae* (isolate B) was recovered from an endotracheal aspirate culture. The patient developed sepsis, multiple organ failure and died at day 56 of her hospitalization.

Susceptibility testing performed and interpreted according to the updated CLSI guidelines [2] showed that *K. pneumoniae* isolates A and B were susceptible only to cefepime, but were resistant to all other β-lactams including carbapenems. The MICs of carbapenems for both isolates determined by E-test (bioMérieux, La Balme-les-Grottes, France) were 8, 8, and 32 mg/L for imipenem, meropenem and ertapenem, respectively. In addition, they were resistant to all aminoglycosides, to fluoroquinolones, nitrofurantoin, chloramphenicol and trimethoprim–sulphamethoxazole. The MICs of tigecycline and colistin of isolate A measured by E-test were 0.25 and 0.094 mg/L, respectively, whereas those of isolate B were 0.25 and 4 mg/L, respectively.

Detection of any carbapenemase activity using the Carba NP test [3] gave a positive result. Therefore, PCR assays were performed to identify the type of carbapenemase produced, with a series of primers designed for the detection of bla_{KPC}, bla_{IMP}, bla_{VIM}, bla_{NDM} and bla_{OXA-48} carbapenemase genes [4], and PCR and sequencing identified the bla_{KPC-2} gene. Pulsed-field gel electrophoresis analysis indicated that both isolates were clonally related, exhibiting identical restriction patterns (data not shown).

Mating-out assays produced an *Escherichia coli* transconjugant expressing KPC-2, exhibiting a reduced susceptibility to carbapenems (MICs of 0.5, 2 and 0.38 mg/L for ertapenem, imipenem and meropenem, respectively), harbouring a single 120-kb plasmid typed as an IncFII by PCR-based replicon typing [5]. Further PCR mapping showed that bla_{KPC-2} was part of transposon Tn*4401b* [1].

Multilocus sequence typing performed as described elsewhere (http://pubmlst.org) identified isolates A and B as belonging to sequence type (ST) 258, being the most commonly identified ST among KPC-producing *K. pneumoniae* worldwide.

The successful spread of the ST258 KPC-2-positive *K. pneumoniae* clone is well recognized. However, it had so far never been identified in Turkey, a country with a specific epidemi-

ology, where OXA-48 carbapenemase has been extensively identified for a decade [1], but only a single report of imported NDM-1-producing *K. pneumoniae* is known [6]. Worryingly, we report here the *in vivo* selection of a colistin-resistant KPC-producing *K. pneumoniae* isolate under combined therapy. That selection occurred in a critically ill patient who later died of that infection. This shows that the current spread of carbapenem non-susceptible isolates is extremely worrisome, considering that colistin will not solve all therapeutic problems.

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Transparency Declarations

None to declare.

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