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Multiclonal outbreak of highly resistant OXA-48-producing *Klebsiella pneumoniae* strains in a tertiary care hospital: attack of the clones

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Background: *Klebsiella pneumoniae* strains producing KPC and MBL carbapenemases are endemic in Greece, whereas the extent of dissemination of OXA-48-producing *K. pneumoniae* (KP-OXA-48) can hardly be estimated. The first outbreak caused by ST11 KP-OXA-48 occurred in 2012 in our hospital and was successfully restrained within 6 months. The present study was conducted from June 2014 (when KP-OXA-48 re-emerged in our setting) to June 2016 and outlines the establishment of KP-OXA-48.

Material/methods: The study involved all KP-OXA-48 strains, isolated from clinical and surveillance specimens during the 2-year study period. Susceptibility testing was performed by Vitek2 and Etest (bioMerieux, France). The screening for carbapenemase production was performed by Modified Hodge Test and combined disc tests using meropenem without and with phenylboronic acid and/or EDTA were applied for carbapenemase differentiation. The *bla*_{OXA-48} and other β -lactamase genes were detected by PCR. Genetic relatedness was assessed by PFGE and MLST.

Results: We studied 227 KP-OXA-48 derived from 79 patients (males 60.8%, median age 61 years). Of them, 67/79 were hospitalized in the ICU; the median time from admission to KP-OXA-48 acquisition was 10 days, with 8/79 patients yielding the isolate during the first 48 hours of hospitalization. The majority of the isolates were considered colonizers (rectal swabs, 41%; central venous catheter tips, 26%), while 33 (14.5%) isolates caused bloodstream infections in 19 patients. The isolates exhibited broad antibiotic resistance profile with non-susceptibility (NS) to carbapenems (99.6%) and expanded spectrum cephalosporins (95.1%). The NS rates to colistin and tigecycline were alarmingly high: 81.9% and 54.1%, respectively. In addition, 94.7% of the study isolates were NS to gentamicin, 61.8% to amikacin and 74.9% to trimethoprim/sulfamethoxazole. The molecular analysis revealed that 80.6% also harbored *bla*_{CTX-M}. Eight KP-OXA-48 isolates co-carried an additional carbapenemase gene: *bla*_{KPC} (n=3), *bla*_{VIM} (n=4), *bla*_{NDM} (n=1). The clonality analysis of 66 selected isolates showed that they were clustered into 3 different PFGE types (A, B, C) that were associated to ST147 (40.9%), ST101 (56.1%) and ST383 (3%), respectively. Noteworthy, 3 patients co-carried isolates belonging to ST147 and ST101 and 1 patient yielded isolates of all 3 clonal types. The ST147 emerged in our hospital from June to December 2014 and was introduced by an index patient directly admitted from another institution. The ST101 first emerged in October 2014 and has been established thereafter. Both ST101 and ST383 were acquired and disseminated intra-hospitally, despite infection control efforts.

Conclusions: The multiclonality of KP-OXA-48 circulating in our hospital implies an endemic situation. Considering their NS to most or all antimicrobials, this evolution is alarming and points out the urgent need for timely detection, continuous surveillance and efficient infection control. As inter-hospital transfers were rather frequent, our data may indicate wide dissemination of KP-OXA-48 in Greece.