Carbapenem resistance in Klebsiella pneumoniae with borderline carbapenem MICs

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Objectives: Carbapenem resistance in Klebsiella pneumoniae (CRKP) may be caused by the presence of carbapenemase enzymes or by other β-lactamase such as ESBL’s enzymes combined with permeability defects. According to international guidelines, carbapenem susceptibility breakpoints should be determined based on MIC measurement alone irrespective of the mechanism. Our objectives were to characterize the resistance mechanisms and examine the effects of these mechanisms on several resistance phenotypes in CRKP with carbapenem MICs that are close to the breakpoints.

Methods: The study compared patient-unique isolates from two populations: 1) carbapenemase-producing CRKP (C-CRPKP) and 2) non-carbapenemase-producing CRKP (NC-CRPKP). Both groups included ertapenem-resistant isolates (MIC≥4 mg/L) that were non-susceptible but not highly resistant to imipenem and/or meropenem (MIC’s range 0.5-4 mg/L). Susceptibility testing was performed by agar dilution, either in standard conditions or after induction by imipenem. Inoculum effect was tested by comparing standard AD MIC measurement (10⁴ inoculum) with 10⁵ and 10⁶ inoculums. Molecular typing was done by pilV-PCR for the identification of the epidemic ST-258 clone and by BOX-PCR. The β-lactamase and the ompK35, ompK36 and ompK37 genes were characterized by PCR and sequencing and their expression was tested by qRT-PCR. We defined a resistance index as the relative expression of the β-lactamase genes divided by the ompK36 expression.

Results: The C-CRPKP group included 24 isolates, with various carbapenemase enzymes (KPC: 6, OXA-48: 15, VIM: 2 and NDM: 1). The NC-CRPKP group included 9 isolates, of various CTX-M enzymes. The clonal structure was diverse, with no more than 2 isolates of the same BOX-PCR pattern, with the exception of three ST-258 KPC-producing isolates. At least one truncated ompK gene was found in 6 of the 9 (66%) NC-CRPKP isolates but in only 5 of the 24 (20.8%) C-CRPKP isolates. The resistance index was highest in the NC-CRPKP isolates (mean-58.2%) compared with 30.3% in the KPC-producers and less than 5% in the other C-CRPKP isolates. Inoculum effect was found in 22 of the 24 (91.6%) C-CRPKP isolates but in only 3 of the 9 (33.3%) NC-CRPKP isolates. Increased meropenem MIC after induction (0.5→2 mg/L) was found in one NC-CRPKP isolate.

Conclusions: NC-CRPKP isolates have higher rate of ompK truncation and higher β-lactamase to ompK36 expression ratio compared with C-CRPKP isolates with comparable carbapenem MIC’s. Respectively, inoculum effect is much more common in C-CRPKP isolates, which may have therapeutic implication in certain high inoculum infections. This suggests that MIC measurements alone without carbapenemase testing may not be sufficient in predicting the therapeutic efficiency of imipenem or meropenem in infections caused by CRKP isolates with borderline resistance to these agents.