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OXA-517, an extended-spectrum cephalosporin- and carbapenem-hydrolysing OXA-48-like variant

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Background: In the last few years the emergence of carbapenem resistance in Gram-negatives has been observed worldwide, both in non-fermenters and in Enterobacteriaceae. The emergence of carbapenemase-producing Enterobacteriaceae (CPE) has become a major public health concern. Among these CPEs, OXA-48-producing Enterobacteriaceae have now widely disseminated throughout European countries. OXA-48 confers high-level resistance to penicillins, including temocillin and hydrolyzes carbapenems at a low level, but spares extended-spectrum cephalosporins. Since the first identification of OXA-48, different variants have been reported, differing by few amino acid substitutions or deletions mostly in the region of the β5-β6 loop. Whereas some OXA-48-variants have similar hydrolytic activities to OXA-48, others, such as OXA-163 or OXA-405 do not present carbapenem-hydrolysis and acquired the capacity of hydrolyze expanded-spectrum cephalosporin. Here we characterized the first OXA-48-like β-lactamase, named OXA-517, able to hydrolyze at the same time expanded-spectrum cephalosporins and carbapenems from a multidrug- resistant *Klebsiella pneumoniae* strain 1219 isolated from Belgium.

Methods: Whole genome sequencing was performed using an Illumina MISeq platform. The functional profile of OXA-517, by the expression of the cloned gene in *Escherichia* coli, was investigated by susceptibility testing and minimal inhibitory concentration (MIC) determination, following EUCAST recommendations. Plasmid characterization and mating-out assay were performed. Steady state parameters of the purified enzyme were determined and compared with those of OXA-48 and OXA-163. Structural analysis was performed.

Results: Sequencing analysis revealed the presence of a novel OXA-48 type β-lactamase gene, named $bla_{OXA-517}$. OXA-517 presents a deletion in Arg-222 and Ile-223 and a substitution Glu-Lys in the position 223 (DBL numbering system). According to the MICs values this protein presented activity against expanded-spectrum cephalosporins as well as carbapenems. The substrate specificity was confirmed by steady state parameters of the purified enzyme, which exhibited high catalytic efficiencies for expanded-spectrum cephalosporins and carbapenems. The $bla_{OXA-517}$ gene was located on a ca. 31-kb plasmid identical to the prototype IncL/M bla_{OXA-48} –carrying plasmid except for a ca.30.7-kb deletion in the *tra* operon, and for the insertion of IS1R.

Conclusions: OXA-517 is the first report of an OXA-48 like β-lactamase capable of hydrolyzing expanded-spectrum cephalosporins and carbapenems at the same time.