P1315
Paper Poster Session
New antibiotics against Gram-negative bacteria

Activity of ceftazidime/avibactam against Enterobacteriaceae producing extended-spectrum beta-lactamases and acquired AmpC beta-lactamases, including those lacking porin expression

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Background: Avibactam (AVI) is a new broad spectrum inhibitor of serine β-lactamases (including classes A, C, and some D) present at increased rates among Enterobacteriaceae. AVI has been recently commercialized in USA in combination with ceftazidime (CAZ). The purpose of this study was to evaluate the activity of CAZ/AVI against a well defined collection of Enterobacteriaceae producing extended-spectrum-beta-lactamases (ESBL) and acquired AmpC-beta-lactamases (AACBL). The role of porin loss, in *Klebsiella pneumoniae* was also assessed.

Material/methods: 100 ESBL-producing *Escherichia coli* and *K. pneumoniae,* from a nationwide study performed in 2006, including the most prevalent ESBLs and clones, 47 *K. pneumoniae* strains producing AACBL, ESBL, or both, expressing or not porins [POR(+)/(-)], and 100 AACBL-producing Enterobacteriaceae from a nationwide study performed in 2009, including the most prevalent species and enzymes, were studied. The *in vitro* activity of CAZ and CAZ/AVI (4 mg/L) was determined by microdilution according to CLSI guidelines and interpreted applying EUCAST breakpoint criteria for CAZ.

Results: 78% and 80% of the ESBL-producing *E. coli* and *K.* pneumoniae isolates from the 2006 nationwide study were resistant (R) to CAZ, respectively, 20% and 10% intermediate, and 2% and 10% susceptible (S) (one *E. coli* producing CTX-M-9 and five *K. pneumoniae* producing CTX-M-type ESBLs). All but two isolates displayed CAZ/AVI MICs ≤1 mg/L. The two isolates of *K. pneumoniae* displaying the highest MICs of CAZ/AVI expressed CTX-M-1, and SHV-12, respectively, with MICs of CAZ/AVI of 2 mg/L and 8 mg/L, respectively. Four *E. coli* isolates belonged to the international clone

ST-131 and showed MICs of CAZ from 4 mg/L to >32 mg/L, whereas those for CAZ/AVI ranged from 0.25 mg/L to 1 mg/L. The 47 isolates of *K. pneumoniae* producing ESBL, AACL or both were CAZ-R, with $MIC_{50/90}$ of >32/>32 mg/L. The addition of AVI reduced $MIC_{50}/_{90}$ to 1 mg/L/ 4 mg/L. MICs of CAZ/AVI ≤ 0.5 mg/L were only observed in isolates POR(+), and all but one of the isolates displaying the highest MICs of CAZ/AVI (4 mg/L) were POR(-). All the AACBL Enterobacteriaceae isolates from the 2009 nationwide study were CAZ-R, with $MIC_{50}/_{90}$ of 32 mg/L/ >32 mg/L. The addition of AVI significantly improved the activity of CAZ, lowering the $MIC_{50}/_{90}$ to 0.25 mg/L/0.5 mg/L. No significant differences were observed in the ability of AVI to protect CAZ from hydrolysis by different types of AACBLs or in different species.

Conclusions: CAZ/AVI displayed an excellent activity against clinical isolates of ESBL-producing *E. coli* and *K. pneumoniae*. The activity against POR(-) isolates of *K. pneumoniae* producing ESBL, AACBL, or both, was retained although MIC values were higher than in POR(+) isolates. AVI restored the activity of CAZ against all AACBL-producing Enterobacteriaceae.