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O0930 Ceftazidime-avibactam activity against a challenge set of carbapenem-resistant Gram-negative clinical isolates and evaluation of resistance mechanisms

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Background: Ceftazidime-avibactam (CAZ-AVI) is an important addition to the armamentarium against multidrug-resistant organisms. This study evaluated CAZ-AVI activity against carbapenem-resistant *Enterobacteriaceae* (CRE) and resistance mechanisms among non-metallo-β-lactamase (MBL) producers.

Materials/methods: 8,165 *Enterobacteriaceae* were recovered from ex-US during the 2016 SENTRY Program and 285 (3.5%) were categorized as CRE. Among CRE, 15 (14 *Klebsiella pneumoniae* and 1 *Enterobacter aerogenes*) showed CAZ-AVI MICs of 2–8 mg/L, did not harbor MBL, and were selected for further investigation. MICs were determined in triplicate in the presence/absence of phenylalanine-arginyl β-naphthylamide (PAβN) and polymyxin B nonapeptide (PMBN). In addition to screening of β-lactamase genes, genome sequences were investigated for the integrity of porin genes and MLST. qRT-PCR assays were conducted to determine expression of porins and *acrA* or *ampC* genes.

Results: Overall, CAZ-AVI (99.2% susceptible) had MIC_{50} and MIC_{90} values of 0.12 mg/L and 0.5 mg/L respectively. These values were similar against Asia-Pacific, European, Latin American, and North American (Canada) isolates. CAZ-AVI inhibited 78.6% (224/285) of all CRE and 100% (226/226) of non-MBL producers at the EUCAST breakpoint (≤8 mg/L). Among the carbapenemase producers (94.2%; 243/285), the most common gene detected was bla_{KPC} at 50.6% (61.8% bla_{KPC-3} and 37.4% bla_{KPC-2}), followed by bla_{OXA-48}-like (24.7%) and bla_{NDM} (20.6%). The bla_{NDM} gene along with bla_{OXA-48}-like were detected in 6 isolates (2.5%). Seven MLSTs were observed among the selected 14 *K. pneumoniae* and 56.3% belonged to clonal complex 258. Clonality was observed among *K. pneumoniae* within a Brazilian and an Italian site. Adding PAβN did not decrease CAZ-AVI MICs, but PMBN significantly decreased the combination MICs to 0.03–0.25 mg/L, except for 2 isolates (MIC, 0.5–1 mg/L). All selected 15 isolates had a premature stop codon at OmpK35 (*K. pneumoniae*) or at OmpC (*E. aerogenes*). Expression of *acrA* among *K. pneumoniae* were comparable to expression of a susceptible control, while *E. aerogenes* overexpressed *ampC.*

Conclusions: The bla_{KPC} gene remained the main carbapenemase observed among ex-US CRE, while bla_{NDM} and bla_{OXA-48}-like occurrences were similar. Generally, elevated CAZ-AVI MIC values (2–8 mg/L) seem to be associated with lack of OmpK35 or OmpC.