28th ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
Madrid, Spain
21 – 24 April 2018

O0933 Effects of Outer Membrane Porin Loss and Presence of Carbapenemases (OXA/KPC) on the In Vitro Activity of Ceftazidime-Avibactam (CZA) against Carbapenem-Resistant Klebsiella pneumoniae (CRKP)

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Background: Loss of two major porins, OmpK35 and OmpK36, has been implicated in carbapenem resistance. Reduced activity of CZA, a recent addition to the armamentarium against carbapenem-resistant KP (CRKP), has been observed in ESBL-producing KPC-2 variant strains of ST258 clone with OmpK36 loss. However, it remains unknown if porin loss is associated with reduced CZA activity for KPC strains of different STs and non-carbapenemase-producing KP (NCKP). We evaluated CZA susceptibilities in a large collection of CRKP with heterogenous resistant mechanisms.

Materials/methods: 116 CRKP clinical isolates with and without porin loss were included. Carbapenemased and ESBLs were elucidated using PCR. OmpK35 and OmpK36 expression were elucidated with western blot. CZA MICs were obtained using Etest®. Categorical interpretation of CZA was applied using EUCAST breakpoint.

Results: All isolates harboured ≥ 1 ESBL type. The KPC-2-KP in our study had various STs: 11, 17, 20, 23, 65,134, 258, 273, 307, 327, 841 and 1304. The median (range) CZA MICs are displayed in Figure 1. The MIC_{50} and MIC_{90} of CZA were 1mg/L and 2mg/L respectively. When stratified by carbapenemase types, all KPC-2-KP were susceptible with low MICs ≤ 2mg/L, even in those with both OmpK35 and OmpK36 loss. Notably, none of the ST258 clones had any porin loss. In OXA-KP, all but 2 isolates had MIC ≤ 2mg/L. The MIC ranges were similar in OXA-KP with and without porin loss. The only OXA-KP isolate with borderline MIC of 8mg/L had no porin loss. Compared to carbapenemase producing KPs, NCKP generally had higher MICs. There were 2 resistant isolates (EC0380 – NCKP with OmpK35 loss, MIC 512 mg/L; EC2239 – NCKP with both OmpK35 and OmpK36 loss, MIC 16 mg/L). All 4 isolates with MIC 8mg/L had OmpK35 loss, but only 2 had OmpK36 loss.

Conclusions: CRKP were highly susceptible to CZA. However, CZA resistance was observed in NCKP. It appeared that porin loss did not contribute to decreased susceptibility in KPC-2-KP and OXA-KP. Decreased CZA susceptibility was observed in NCKP, particularly those with OmpK35 loss.

CRKP types	Porin mechanism	No of isolates	CZA MIC (ug/mL)		No of isolates with MIC ≥8 mg/L
			Median	Range	
NCKP	All	56	1	0.25 - 512	4
	OmpK35 loss	13	1	0.25 - 512	2
	OmpK36 loss	5	0.5	0.25 - 1	0
	Both loss	34	1	0.25 - 16	2
	Neither loss	4	2	0.25 - 2	0
KPC-2-KP	All	38	1	0.25 - 2	0
	OmpK35 loss	14	1	0.25 - 2	0
	OmpK36 loss	1	1	-	0
	Both loss	8	1	0.5 - 2	0
	Neither loss	15	0.5	0.25 - 2	0
OXA-KP	All	22	1	0.12 - 8	0
	OmpK35 loss	7	0.5	0.25 - 1	0
	OmpK36 loss	0	-	-	-
	Both loss	4	2	0.5 - 4	0
	Neither loss	11	2	0.125 - 8	1

Figure 1. CZA MICs of among different CRKP