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

P0096 Evaluation of apramycin activity against carbapenem-resistant Enterobacteriaceae and Acinetobacter baumannii

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Background: In the paucity of novel classes of antimicrobials with activity against multidrug resistant Gram-negatives, there is a need for re-investigation of existing drug classes to identify already known, potentially active molecules that could be modified and/or tested for clinical use. We evaluated the in vitro activity of apramycin, a structurally unique aminoglycoside currently used in veterinary medicine, against aminoglycoside-resistant Enterobacteriaceae and *A.baumannii* isolates collected from different Greek hospitals.

Materials/methods: A collection of 411 carbapenem-resistant Enterobacteriaceae (CRE) as well as 594 carbapenem-resistant *A.baumannii* (CRAB), collected from 18 Greek hospitals, known to be resistant to all clinically approved aminoglycosides (AR) were tested for their susceptibility to apramycin. Apramycin, amikacin, gentamicin and tobramycin were tested against all strains using the broth microdilution method according to CLSI guidelines. All experiments included *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 as quality control strains. Production of 16S rRNA-methylases and carbapenemases was confirmed by multiplex PCR.

Results: Apramycin demonstrated an MIC50/MIC90 of 8/32 mg/L against AR-CRE, regardless of 16S-rRNA-methylase production, 32/64 mg/L against *armA*- and 16/32 against non-*armA*- AR-CRAB. Apramycin inhibited 88.6% of CRAB and 94.9% of CRE (96.4% of *K.pneumoniae*, 94.6% of *P.stuartii* and 74.1% of *P.mirabilis*) at a concentration of ≤32mg/L, which is the apramycin breakpoint of susceptibility per National Antimicrobial Resistance Monitoring System (NARMS).

Conclusions: Apramycin appears to offer promising in vitro activity against carbapenemase-producing pathogens, including CRE and CRAB, and demonstrated a remarkable superiority over all other aminoglycosides in clinical practice. Apramycin appears worthy of further investigation for re-purposing as a human therapeutic; its unique nucleus may provide the scaffold for future derivatives that overcome methylase-mediated resistance.

Table. Apramycin susceptibility data for Enterobacteriaceae and *Acinetobacter baumannii* strains resistant to all clinically approved aminoglycosides

Isolates resistant to clinically approved aminoglycosides		n	MIC mg/L			MIC ≤32mg/L n (%)
			Range	MIC_{50}	MIC_{90}	
Klebsiella pneumoniae	Total	309	2-128	8	16	298 (96.4%)
	RMT(+)	139	2-64	8	16	135 (97.1%)
	RMT(-)	170	2-128	8	16	163 (95.9%)
Proteus mirabilis	Total	27	4->512	16	128	20 (74.1%)
	RMT(+)	15	16-128	16	64	12 (80.0%)
	RMT(-)	12	4->512	32	>512	8 (66.7%)
Providencia stuartii	Total	55	2-128	16	32	52 (94.6%)
	RMT(+)	52	2-128	16	32	49 (94.2%)
	RMT(-)	3	16-32	ND	ND	3 (100%)
Other Enterobacteriaceae	Total	20	4-32	8	32	20 (100%)
	RMT(+)	3	8	ND	ND	3 (100%)
	RMT(-)	17	4-32	8	32	17 (100%)
Acinetobacter baumannii	Total	594	2-256	16	64	526 (88.6%)
	RMT(+)	308	4-256	32	64	267 (86.7%)
	RMT(-)	286	2-256	16	32	259 (90.6%)
Quality control						
Escherichia coli ATCC® 25922		36	4-8	-	-	-
Pseudomonas aeruginosa ATCC® 27853		36	4-8	-	-	-