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### Plazomicin activity against European Enterobacteriaceae isolates carrying aminoglycoside-modifying enzymes and 16S rRNA methylases

Mariana Castanheira\*<sup>1</sup>, Timothy Doyle<sup>1</sup>, Leah N. Woosley<sup>1</sup>, Alisa Serio<sup>2</sup>, Kevin Krause<sup>3</sup>, Robert Flamm<sup>1</sup>

<sup>1</sup>*Jmi Laboratories*

<sup>2</sup>*Achaogen Inc.; Microbiology*

<sup>3</sup>*Achaogen, Inc.; Microbiology*

**Background:** Production of aminoglycoside-modifying enzymes (AME) is the most frequent aminoglycoside resistance mechanism in Enterobacteriaceae. Although 16S rRNA methylases (RNAmet) are not as common, they confer high level resistance against virtually all aminoglycosides. We evaluated the occurrence of AME and RNAmet among aminoglycoside non-susceptible Enterobacteriaceae isolates collected in 26 European countries during 2014-2015 and the activity of plazomicin (PLZ) and comparators against these isolates.

**Material/methods:** Enterobacteriaceae isolates (n=4,217) from 49 European hospitals were susceptibility tested using reference broth microdilution method. Isolates displaying non-susceptible MICs (CLSI criteria) for gentamicin (GEN) and/or amikacin (AMK) and/or tobramycin (TOB) were screened for *aac(6′)-Ib*, *aac(3)-IIa*, *ant(2′′)-Ia*, *aph(3′)-Via*, *aac(3)-I-like*, and *aac(3)-IVa*. Isolates displaying PLZ MIC results at ≥128 µg/mL were tested for RNAmet.

**Results:** Among 799 (18.9% overall) isolates tested for AMEs, 583 carried *aac(6′)-Ib*, 446 carried *aac(3)-IIa*, 40 carried *ant(2′′)-Ia*, and 20 isolates carried four other genes: *aac(3)-IVa*, *aac(3)-Ia*, *aac(3)-Id/e*, and *aph3-VIa*. Combinations of these genes were detected among 348 isolates and the most common was *aac(6′)-Ib-aac(3)-IIa* (318 isolates). Only 72 (9.0%) isolates were negative for AME genes tested. AME producers were more common in Poland (70.2% of collected isolates), Ukraine (62.5%), Russia (40.0%), Romania (37.5%) and Turkey (29.5%). AME genes were mainly detected among *Klebsiella pneumoniae* (466/503) and *Escherichia coli* (216/233), but also in 5 other species. RNAmet were detected among 59 of 60 (1.4% overall) isolates displaying resistance to all aminoglycoside and PLZ MIC values of ≥128 mg/L (23 *rmtB*, 16 *armA* [one also carrying *rmtA*], 12

*rmtC*, 8 *rmtF*). PLZ inhibited 720/727 (99.0%) isolates harbouring AME genes at  $\leq 2$  mg/L and 21/81 isolates non-susceptible to all aminoglycoside displayed PLZ MICs ranging from 0.25 to 4 mg/L. Among the 7 AME-producers displaying PLZ MIC values of 4-16 mg/L, there were 3 *K. pneumoniae*, 2 *E. coli* and 2 *Proteus mirabilis*. Only two isolates were AMK non-susceptible and displayed PLZ MICs of 0.5 and 4 mg/L. RNAmet producers displayed high MICs to all aminoglycosides.

**Conclusions:** PLZ showed stability against common AME genes detected in European countries and was more active than AMK, GEN or TOB against AME-producing isolates. RNAmet producers were uncommon and R to all aminoglycosides. This data supports the current development plan for plazomicin for the treatment of serious infections caused by resistant Enterobacteriaceae where treatment options are limited.

Isolate Groups (no. tested)	MIC <sub>50</sub> /MIC <sub>90</sub> (mg/L)			
	PLZ	AMK	GEN	TOB
All Enterobacteriaceae (4,217)	0.5/1	1/4	0.5/1	0.5/1
Only GEN-non-susceptible (74)	0.5/4	1/2	>8/>8	4/4
Only TOB-non-susceptible (203)	0.25/1	4/16	0.5/2	>8/>8
GEN+TOB-non-susceptible (474)	0.25/1	4/16	>8/>8	>8/>8
AMK+TOB-non-susceptible (68)	0.5/1	32/>32	1/2	>8/>8
AMK+GEN+TOB-non-susceptible (81)	>128/>128	>32/>32	>8/>8	>8/>8
<i>aac(6')-Ib</i> (583)	0.25/1	4/32	>8/>8	>8/>8
<i>aac(3)-IIa</i> (446)	0.25/1	4/16	>8/>8	>8/>8
<i>ant(2'')-Ia</i> (40)	0.25/2	2/8	>8/>8	>8/>8
RNAmet (59)	>128/>128	>32/>32	>8/>8	>8/>8