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Antimicrobial Activity of Plazomicin Tested against a Worldwide Collection of *Enterobacterales* Isolated from Patients with Complicated Urinary Tract Infections (2014–2017)

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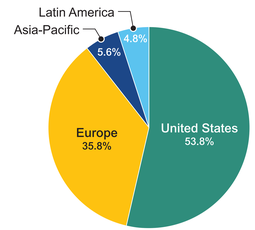
Introduction

- Plazomicin is a novel semisynthetic parenteral aminoglycoside that inhibits bacterial protein synthesis
- Plazomicin was approved by the United States Food and Drug Administration (US FDA) for use in adults with complicated urinary tract infections (cUTIs), including pyelonephritis
- Plazomicin displays potent *in vitro* activity against *Enterobacterales*, including both extended-spectrum β-lactamase (ESBL)-producing and carbapenem-resistant (CRE) isolates
- The enhanced *Enterobacterales* activity exhibited by plazomicin is due to its stability to commonly encountered aminoglycoside-modifying enzymes that compromise the activity of traditional aminoglycosides
- We evaluated the *in vitro* activity of plazomicin against clinical isolates collected from patients with cUTIs worldwide from 2014 through 2017

Materials and Methods

- A total of 4,657 *Enterobacterales* (1/patient) isolates were collected from medical centers in the United States (USA; n=2,508; 60 centers), Europe (EUR; n=1,667; 33 centers in 17 nations), Asia-Pacific (APAC; n=260; 13 centers in 7 nations), and Latin America (LATAM; n=222; 10 centers in 6 nations) in 2014–2017 (Figure 1)
- Plazomicin and comparator agents were susceptibility tested by reference broth microdilution methods at a central laboratory (JMI Laboratories, North Liberty, Iowa, USA)
- US Food and Drug Administration categorical interpretations were applied for plazomicin, and interpretations from the Clinical and Laboratory Standards Institute (CLSI) and/or US FDA breakpoint tables were applied for comparator agents, when available
- CRE was defined as any isolate exhibiting resistance (CLSI) to doripenem, imipenem, and/or meropenem (MIC values at ≥4 mg/L; imipenem was not applied for *Proteus mirabilis* and indole-positive Proteeae due to intrinsically elevated imipenem MIC values)
- Multidrug-resistant (MDR) and extensively drug-resistant (XDR) *Enterobacterales* and *Pseudomonas aeruginosa* strains were classified according to recommended guidelines (Magiorakos et al., 2012)
  - MDR = nonsusceptible (NS; CLSI breakpoints) to at least 3 antimicrobial classes
  - XDR = susceptible (S) to 2 or fewer antimicrobial classes
- Quality control (QC) was performed according to CLSI guidelines (M07), and all QC MIC results were within acceptable ranges as published in CLSI documents

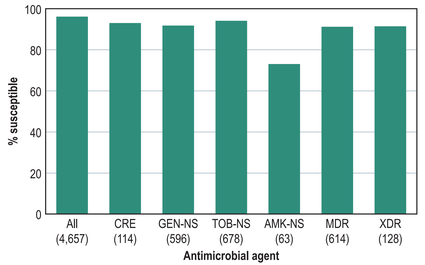
Figure 1 Isolate distribution by geographic region



Results

- Plazomicin exhibited potent activity against *Enterobacterales* from all geographic regions with $MIC_{50/90}$ values of 0.5/2 mg/L and susceptibility rates varying from 94.1% in LATAM to 96.3% in EUR; 96.1%S overall (Table 1)
- Plazomicin was highly active against CRE, with $MIC_{50/90}$ values of 0.5/1 mg/L and susceptibility rates ranging from 100.0% in the USA to 76.2% in LATAM; 93.0%S overall (Table 1; Figures 2 and 3)
- Plazomicin retained activity against most gentamicin-nonsusceptible ($MIC_{50/90}$, 0.5/2 mg/L; 91.8%S), tobramycin-nonsusceptible ($MIC_{50/90}$, 0.5/2 mg/L; 94.1%S), and amikacin-nonsusceptible isolates ($MIC_{50/90}$, 0.5/>128 mg/L; 73.0%S; Figure 2)
- The plazomicin MIC_{50} value was 4-fold lower than that of amikacin and equal to those of gentamicin and tobramycin against all *Enterobacterales* (Table 1)
- Susceptibility rates in 2014 and 2017 were 95.1%/96.2% for plazomicin, 98.8%/98.3% for amikacin, 87.8%/85.2% for gentamicin, 87.3%/82.1% for tobramycin, and 81.1%/76.0% for ceftriaxone (data not shown)
- The *Enterobacterales* species most susceptible to plazomicin (lowest MIC values) were *Klebsiella pneumoniae*, *Enterobacter cloacae*, and *Citrobacter koseri* ($MIC_{50/90}$, 0.25/0.5 mg/L), followed by *Klebsiella oxytoca*, *K. aerogenes*, and *Citrobacter freundii* ($MIC_{50/90}$, 0.5/0.5 mg/L; data not shown)
- Susceptibility rates for amikacin, gentamicin, tobramycin, and other comparators were generally highest in the USA and lowest in LATAM (Table 1)

Figure 2 Plazomicin susceptibility rates for all *Enterobacterales* and resistant subsets collected from patients worldwide with complicated urinary tract infections



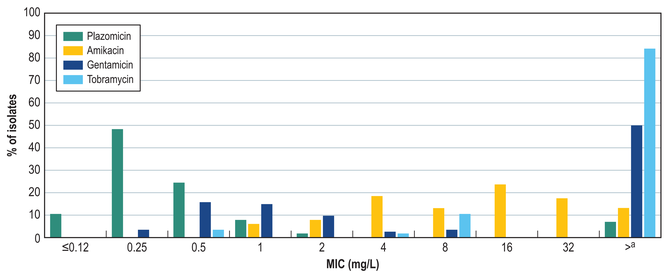
CRE, carbapenem-resistant *Enterobacterales*; GEN-NS, gentamicin-nonsusceptible by CLSI standards; TOB-NS, tobramycin-nonsusceptible by CLSI standards; AMK-NS, amikacin-nonsusceptible; MDR, multidrug-resistant; XDR, extensively drug-resistant.

Table 1 Antimicrobial activity of plazomicin and comparator agents tested against 4,657 *Enterobacterales* isolates

Antimicrobial agent	MIC_{50}	MIC_{90}	% susceptible[a] (no. of isolates)[b]				
			USA	EUR	APAC	LATAM	All
All isolates			(2,508)	(1,667)	(260)	(222)	(4,657)
Plazomicin[c]	0.5	2	96.2	96.3	94.6	94.1	96.1
Amikacin	2	4	98.9	98.8	98.8	94.6	98.6
Gentamicin	0.5	>8	90.2	85.6	85.4	67.6	87.2
Tobramycin	0.5	>8	90.7	81.2	83.5	60.4	85.4
Ceftriaxone	≤0.06	>8	85.9	73.9	73.5	57.7	79.6
Piperacillin-tazobactam	2	16	94.5	85.7	91.1	80.6	90.5
Meropenem	0.03	0.06	98.6	96.5	97.7	90.1	97.4
Levofloxacin	≤0.12	>4	79.5	72.3	75.8	50.5	75.3
Tigecycline[c]	0.25	1	98.3	98.3	96.2	97.7	98.2
Colistin[d]	≤0.5	>8	84.3	85.7	86.9	89.2	85.2
Carbapenem-resistant *Enterobacterales*			(32)	(55)	(6)	(21)	(114)
Plazomicin[c]	0.5	1	100.0	96.4	83.3	76.2	93.0
Amikacin	16	>32	53.1	78.2	83.3	66.7	69.3
Gentamicin	8	>8	50.0	47.3	50.0	38.1	46.5
Tobramycin	>8	>8	3.1	7.3	16.7	0.0	5.3
Levofloxacin	>4	>4	6.2	3.6	16.7	0.0	4.4
Tigecycline[c]	0.5	2	100.0	98.2	100.0	95.2	98.2
Colistin[d]	≤0.5	>8	75.0	67.3	83.3	71.4	71.1
Multidrug-resistant *Enterobacterales*			(217)	(281)	(39)	(77)	(614)
Plazomicin[c]	0.5	2	88.0	94.0	94.9	88.3	91.2
Amikacin	4	16	88.0	93.2	97.4	87.0	90.9
Gentamicin	>8	>8	38.2	41.6	35.9	23.4	37.8
Tobramycin	>8	>8	29.5	16.7	15.4	6.5	19.9
Ceftriaxone	>8	>8	17.5	8.9	7.7	5.2	11.4
Piperacillin-tazobactam	32	>64	59.4	37.4	48.7	46.8	47.1
Meropenem	0.06	16	84.3	79.4	84.6	71.4	80.5
Levofloxacin	>4	>4	5.5	3.2	7.7	3.9	4.4
Tigecycline[c]	0.5	2	89.4	97.2	97.4	98.7	94.6
Colistin[d]	≤0.5	>8	68.2	78.1	87.2	87.0	76.3
Extensively drug-resistant *Enterobacterales*			(34)	(67)	(5)	(22)	(128)
Plazomicin[c]	0.5	2	100.0	94.0	60.0	77.3	91.4
Amikacin	16	>32	55.9	80.6	80.0	68.2	71.9
Gentamicin	>8	>8	50.0	41.8	40.0	40.9	43.8
Tobramycin	>8	>8	5.9	3.0	20.0	0.0	3.9
Ceftriaxone	>8	>8	2.9	0.0	0.0	0.0	0.8
Piperacillin-tazobactam	>64	>64	5.9	3.0	0.0	0.0	3.1
Meropenem	8	>32	11.8	17.9	20.0	0.0	13.3
Levofloxacin	>4	>4	2.9	0.0	0.0	0.0	0.8
Tigecycline[c]	0.5	2	94.1	95.5	100.0	95.5	95.3
Colistin[d]	≤0.5	>8	67.6	59.7	80.0	68.2	64.1

USA, United States; EUR, Europe; APAC, Asia-Pacific region; LATAM, Latin America
[a] Criteria as published by CLSI 2019.
[b] FDA breakpoints published 2018-JUN-26.
[c] FDA breakpoints accessed January 2019.
[d] EUCAST breakpoint (2019).

Figure 3 MIC distributions for plazomicin, amikacin, gentamicin, and tobramycin when tested against carbapenem-resistant *Enterobacterales* isolates



[a] Greater than the highest dilution tested.

Conclusions

- Plazomicin demonstrated potent activity against a large collection of worldwide *Enterobacterales* isolates collected from patients with cUTIs and the agent had 4-fold lower MIC values when compared to amikacin
- Plazomicin activity was consistent but susceptibility rates for comparators varied by geography and were generally higher in the USA than in other geographic regions

Acknowledgements

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