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Antimicrobial Activity of Plazomicin Tested against Enterobacteriaceae Isolates from European Medical Centres Stratified by Infection Type (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 Enterobacteriaceae, including both extended-spectrum ß-lactamase (ESBL)-producing and carbapenem-resistant (CRE) isolates
- The enhanced Enterobacteriaceae 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 in European medical centres from 2014 through 2017

Materials and Methods

- A total of 8,228 Enterobacteriaceae (1/patient) isolates were collected from medical centres located in Western Europe (W-EUR; n=6,535; 32 centres in 16 nations) and Eastern Europe (E-EUR; n=1,693; 14 centres in 10 nations) in 2014–2017
- Isolates were from bloodstream infections (BSIs; 33.3%), pneumonia (22.5%), cUTIs (20.3%), skin and skin structure infections (SSSIs; 14.3%), and intra-abdominal infections (IAIs; 9.1%)
- Plazomicin and comparator agents were susceptibility tested by reference broth microdilution methods at a central laboratory (JMI Laboratories, North Liberty, Iowa, USA)
- US FDA categorical interpretations were applied for plazomicin, and interpretations from the EUCAST and CLSI breakpoint tables were applied for comparator agents
- CRE was defined as any isolate exhibiting doripenem, imipenem, and/or meropenem MIC values at ≥2 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) Enterobacteriaceae and *P. 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

Results

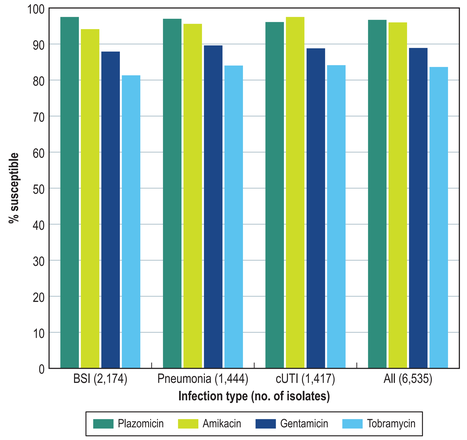
- Overall, 95.9% of Enterobacteriaceae were inhibited at a plazomicin MIC of ≤2 mg/L, which is the susceptible breakpoint established by the US FDA, varying from 96.7% in W-EUR to 93.0% in E-EUR ($MIC_{50/90}$, 0.5/2 mg/L in both regions; Tables 1 and 2)
- Enterobacteriaceae susceptibility rates to plazomicin in W-EUR/E-EUR were 96.1%/97.6% for cUTI, 97.5%/93.3% for BSI, 97.0%/90.0% for pneumonia, 97.7%/96.6% for IAI, and 94.4%/91.2% for SSSI isolates (data for cUTI, BSI, and pneumonia displayed in Figures 1 and 2)
- Plazomicin retained good *in vitro* activity against ESBL-phenotype (94.4% susceptible at ≤2 mg/L), CRE (83.2% susceptible), MDR (89.9% susceptible), and gentamicin-nonsusceptible (NS; 86.3% susceptible) isolates for Europe overall (data not shown), but variation was observed between W-EUR and E-EUR (Tables 1 and 2)
- CRE rates varied by infection type: 2.8% for cUTI, 6.3% for BSI, 6.4% for pneumonia, 4.0% for IAI, and 3.2% for SSSI (data not shown)
- ESBL-phenotype and MDR rates were also higher among isolates from pneumonia and BSI compared to other infection types (data not shown)
- The most active comparator agents tested were the carbapenems (94.9% susceptible to meropenem overall; 96.6%/88.4% susceptible in W-EUR/E-EUR), amikacin (94.2% susceptible; 96.0%/87.1% susceptible in W-EUR/E-EUR), and tigecycline (93.6% susceptible; 93.7%/93.1% susceptible in W-EUR/E-EUR; Table 2)
- Meropenem susceptibility varied from 96.9% for SSSI and UTI to 93.5% for BSI and pneumonia, and amikacin susceptibility ranged from 95.9% for SSSI to 93.0% for pneumonia (data not shown)

Table 1 Antimicrobial activity of plazomicin and Enterobacteriaceae isolates and resistant subsets from European hospitals (2014–2017)

Geographic region / Organism/organism group (n)	Cumulative % inhibited at plazomicin MIC (mg/L) of: ≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128	MIC (mg/L) 50%	90%
Western Europe															
Enterobacteriaceae (6,535)	0.2	4.5	35.8	70.9	90.0	96.7	99.1	99.5	99.6	99.6	99.6	99.8	100.0	0.5	2
ESBL-phenotype (1,156)	0.6	7.7	46.3	77.0	94.4	97.2	97.8	97.8	97.9	97.9	97.9	99.0	100.0	0.5	1
CRE (222)	0.9	9.9	58.1	77.9	87.4	90.5	91.0	91.0	91.0	91.0	91.0	96.4	100.0	0.25	2
MDR (1,046)	0.6	8.3	44.1	67.3	83.0	91.1	95.7	97.0	97.2	97.2	97.2	98.5	100.0	0.5	2
XDR (280)	1.1	10.4	56.1	73.2	82.9	88.6	91.1	92.1	92.1	92.1	92.1	96.4	100.0	0.25	4
Gentamicin-NS (725)	0.4	6.1	40.0	64.0	81.5	89.4	93.9	95.6	96.0	96.0	96.0	97.8	100.0	0.5	4
Tobramycin-NS (1,069)	0.5	7.3	43.0	67.9	86.3	93.0	96.1	97.0	97.3	97.3	97.3	98.5	100.0	0.5	2
Amikacin-NS (261)	0.0	3.1	40.2	62.5	79.7	84.7	88.9	89.3	89.3	89.3	89.3	93.9	100.0	0.5	128
Eastern Europe															
Enterobacteriaceae (1,693)	0.2	7.2	48.4	74.6	89.0	93.0	94.8	95.1	95.2	95.2	95.2	96.3	100.0	0.5	2
ESBL-phenotype (832)	0.4	9.1	58.1	77.9	87.9	90.5	90.6	90.7	91.0	91.0	91.0	93.3	100.0	0.25	2
CRE (183)	0.0	4.9	55.2	69.9	74.3	74.3	74.3	74.9	76.0	76.0	76.0	82.0	100.0	0.25	>128
MDR (751)	0.4	8.7	56.7	74.2	82.8	86.4	88.5	89.1	89.3	89.3	89.3	91.9	100.0	0.25	128
XDR (253)	0.0	8.3	57.7	70.4	75.9	78.7	79.1	79.8	80.6	80.6	80.6	85.8	100.0	0.25	>128
Gentamicin-NS (552)	0.4	8.2	52.4	71.2	79.2	82.2	84.2	85.0	85.3	85.3	85.3	88.8	100.0	0.25	>128
Tobramycin-NS (768)	0.3	8.9	57.2	76.2	84.4	87.4	88.7	89.2	89.5	89.5	89.5	91.9	100.0	0.25	128
Amikacin-NS (218)	0.0	1.8	32.6	50.5	58.7	61.0	61.5	61.9	62.8	62.8	62.8	71.6	100.0	0.5	>128

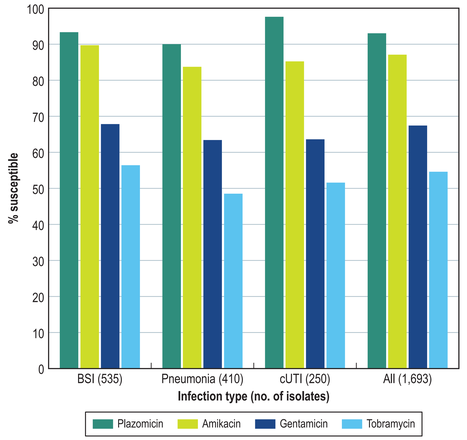
Abbreviations: ESBL, extended-spectrum ß-lactamase; CRE, carbapenem-resistant Enterobacteriaceae; MDR, multidrug-resistant; XDR, extensively drug-resistant; NS, nonsusceptible.

Figure 1 Plazomicin susceptibility rates for Enterobacteriaceae isolates from Western Europe stratified by infection type



BSI, bloodstream infection; cUTI, complicated urinary tract infection

Figure 2 Plazomicin susceptibility rates for Enterobacteriaceae isolates from Eastern Europe stratified by infection type



BSI, bloodstream infection; cUTI, complicated urinary tract infection

Table 2 Antimicrobial activity of plazomicin and comparator agents tested against Enterobacteriaceae isolates from Western and Eastern Europe

Organism/organism group (no. tested in W-EUR/E-EUR) / Antimicrobial agent	Western Europe CLSI[a] %S	CLSI[a] %R	EUCAST[a] %S	EUCAST[a] %R	Eastern Europe CLSI[a] %S	CLSI[a] %R	EUCAST[a] %S	EUCAST[a] %R
Enterobacteriaceae (6,535/1,693)								
Plazomicin	96.7 [b]	0.9			93.0 [b]	5.2		
Amikacin	97.5	0.8	96.0	2.5	92.7	5.4	87.1	7.3
Gentamicin	89.6	9.9	88.9	10.4	68.2	31.2	67.4	31.8
Tobramycin	85.9	10.9	83.6	14.1	57.7	34.6	54.6	42.3
Cefepime	85.0	12.4	83.4	13.8	51.8	45.2	50.2	46.6
Ceftazidime	83.2	14.9	79.4	16.8	51.7	45.2	48.4	48.3
Ceftriaxone	77.9	21.0	77.9	21.0	46.7	52.7	46.7	52.7
Imipenem	89.4	4.5	95.5	2.7	83.3	10.0	90.0	4.4
Meropenem	96.4	3.4	96.6	2.9	86.7	11.6	88.4	6.3
Piperacillin-tazobactam	87.4	8.0	83.2	12.6	65.5	25.3	58.8	34.5
Colistin			83.9	16.1			85.1	14.9
Tigecycline	98.3 [c]	0.2	93.7	1.7	98.3 [c]	0.1	93.1	1.7
Levofloxacin	81.3	16.7	77.1	20.5	58.9	36.3	51.1	43.9
ESBL-phenotype (1,156/832)								
Plazomicin	97.2	2.2 [b]			90.5	9.4 [b]		
Amikacin	86.9	4.2	80.5	13.1	85.8	10.3	75.2	14.2
Gentamicin	62.8	35.9	61.7	37.2	44.2	55.3	43.5	55.8
Tobramycin	41.1	49.0	37.3	58.9	23.8	64.5	20.3	76.2
Imipenem	78.9	18.7	81.3	15.1	75.4	18.8	81.2	8.8
Meropenem	80.6	18.5	81.5	16.0	73.7	23.1	76.9	12.7
Piperacillin-tazobactam	53.3	35.3	42.5	46.7	39.4	45.9	29.6	60.6
Colistin			90.9	9.1			88.4	11.6
Tigecycline	98.0 [c]	0.3	92.8	2.0	98.4 [c]	0.1	93.0	1.6
Levofloxacin	35.9	60.2	27.6	67.4	29.1	63.9	19.9	74.0
CRE (222/183)								
Plazomicin	90.5 [b]	9.0			74.3 [b]	25.7		
Amikacin	42.8	17.6	30.2	57.2	62.3	27.3	45.9	37.7
Gentamicin	68.5	28.8	65.3	31.5	30.6	68.9	30.1	69.4
Tobramycin	12.6	82.0	10.4	87.4	7.1	86.9	5.5	92.9
Colistin			73.3	26.7			68.0	32.0
Tigecycline	97.3 [c]	0.5	84.6	2.7	98.9 [c]	0.0	89.6	1.1
Levofloxacin	8.1	90.1	3.6	94.1	12.6	84.7	5.5	89.6

[a] Criteria as published by CLSI 2018 and EUCAST 2018.
[b] US FDA breakpoints published 2018-JUN-26.
[c] US FDA breakpoints accessed December 2018.
Abbreviations: %S, percentage susceptible; %R, percentage resistant; W-EUR, Western Europe; E-EUR, Eastern Europe; ESBL, extended-spectrum ß-lactamase; CRE, carbapenem-resistant Enterobacteriaceae.

Conclusions

- Plazomicin demonstrated potent activity and was slightly more active than amikacin against European Enterobacteriaceae isolates
- Susceptibility rates varied widely between W-EUR and E-EUR and were generally lower in E-EUR
- Susceptibility rates also varied by infection type and were generally lower among pneumonia isolates

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