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Impact of Different Breakpoint Criteria on the Susceptibility Rates of *Enterobacterales*-Resistant Subsets to the Aminoglycosides

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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.
- Plazomicin's enhanced activity against *Enterobacterales* is due to plazomicin's stability to enzymes that compromise the activity of traditional aminoglycosides.
- We evaluated the susceptibility rates of plazomicin, amikacin, gentamicin, and tobramycin by applying current breakpoints published by different organizations against *Enterobacterales* isolates collected worldwide in 2018–2019.

Materials and Methods

- A total of 9,303 *Enterobacterales* (ENT) isolates (1/patient) were collected in 2018–2019 from medical centers located in the US (n=3,899; 33 centers), Europe (n=3,782; 39 centers in 19 nations), Asia-Pacific (n=795; 13 centers in 7 nations [2018 only]), and Latin America (n=827; 10 centers in 6 nations [2018 only]).
- Isolates were susceptibility tested by reference broth microdilution methods in a central monitoring laboratory (JMI Laboratories).
- Breakpoints for the following organizations were applied when available: Clinical and Laboratory Standards Institute (CLSI), European Committee on Antimicrobial Susceptibility Testing (EUCAST), United States Committee on Antimicrobial Susceptibility Testing (USCAST), and US FDA.
- Isolates were mainly from cUTI (45.9%), bloodstream infections (23.7%), and pneumonia (18.7%).
- 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).
- The ESBL phenotype was defined for *Escherichia coli*, *K. pneumoniae,* and *P. mirabilis* as an MIC value ≥2 mg/L for ceftriaxone, ceftazidime, and/or aztreonam.
- Multidrug-resistant (MDR) strains were defined as nonsusceptible (CLSI) to at least 3 antimicrobial classes. Extensively drug-resistant (XDR) strains were defined as susceptible to 2 or fewer antimicrobial classes.
- Quality control was performed according to CLSI (M07; 2018) guidelines.

Results

- Plazomicin was active against 96.6% and 99.4% of US isolates as per US FDA (≤2 mg/L) and USCAST (≤4 mg/L) criteria, respectively (Table 1).
- Against the worldwide collection of *Enterobacterales*, plazomicin was active against 95.5% and 98.0% of isolates as per US FDA and USCAST criteria, respectively (Table 2).
- CLSI and US FDA breakpoints were identical for the older aminoglycosides (amikacin, gentamicin, and tobramycin), and EUCAST breakpoints were identical for gentamicin and tobramycin and 1 doubling dilution higher for amikacin when compared with USCAST (Tables 1 and 2).
- MIC values were lowest for plazomicin (mode of 0.25 mg/L in the US), followed by gentamicin (mode of 0.5 mg/L) and amikacin (mode 2 mg/L; Figure 1).
- Plazomicin retained potent activity against CRE (Figure 2), ESBL-phenotype, MDR, and XDR isolates (Tables 1 and 2).
- When tested against *Enterobacterales* isolates from the US, susceptibility rates as per US FDA/CLSI and USCAST criteria were 99.4% and 95.2% for amikacin, 91.8% and 90.9% for gentamicin, and 90.7% and 88.2% for tobramycin, respectively (Table 1).
- Against the worldwide collection, susceptibility rates as per US FDA and USCAST criteria were 97.4% and 90.2% for amikacin, 86.4% and 85.6% for gentamicin, and 83.8% and 81.1% for tobramycin, respectively (Table 2).
- CRE susceptibility rates to plazomicin and amikacin in the US were 97.7% and 75.0%, respectively, per US FDA criteria, and 97.7% and 65.9% per USCAST criteria, respectively (Figure 3).
- Differences in susceptibility rates between plazomicin and amikacin were higher when applying USCAST for resistant subsets, such as MDR from US (97.7% versus 70.1%, respectively) and CRE (97.7% versus 65.9%, respectively; Figure 3).
- Gentamicin and tobramycin exhibited limited activity against *Enterobacterales* resistant subsets (Tables 1 and 2).
- Plazomicin ($MIC_{50/90}$, 0.5/1 mg/L) was 4-fold more active than amikacin ($MIC_{50/90}$, 2/4 mg/L) based on MIC_{50} and MIC_{90} values (data not shown).

Conclusions

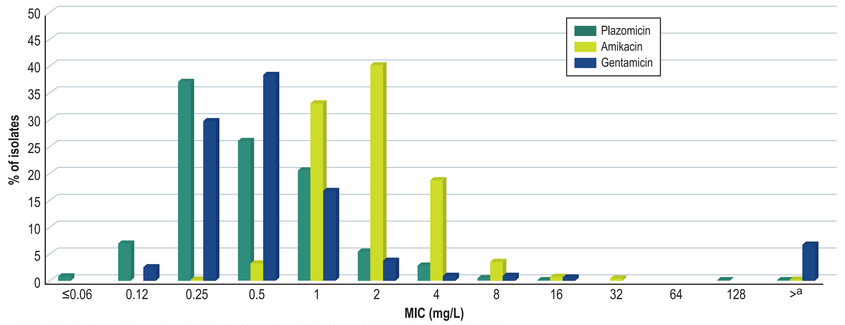
- Plazomicin retained potent activity against *Enterobacterales*, including resistant subsets.
- The discrepancies among the susceptibility rates for aminoglycosides were greater when applying breakpoints generated using the same stringent contemporary methods applied to determine plazomicin breakpoints.
- Moreover, the discrepancies among the susceptibility rates for aminoglycosides were greater for resistant subsets when compared to the entire *Enterobacterales* collection.
- Plazomicin represents a valuable new treatment option for infections caused by *Enterobacterales*, including CRE and MDR isolates.

Table 1 Susceptibility rates for aminoglycosides against *Enterobacterales* isolates from US hospitals applying different breakpoint criteria (2018–2019)

Breakpoint setting organization/ organism group (number tested)	% Susceptible			
	Plazomicin	Amikacin	Gentamicin	Tobramycin
Susceptibility breakpoints (mg/L)				
CLSI	NA	≤16	≤4	≤4
EUCAST	NA	≤8	≤2	≤2
USCAST	≤4	≤4	≤2	≤2
US FDA	≤2	≤16	≤4	≤4
Percent susceptible				
All *Enterobacterales* (3,899)				
CLSI	NA	99.4	91.8	90.7
EUCAST	NA	98.7	90.9	88.2
USCAST	99.4	95.2	90.9	88.2
US FDA	96.6	99.4	91.8	90.7
CRE (44)				
CLSI	NA	75.0	47.7	25.0
EUCAST	NA	68.2	43.2	25.0
USCAST	97.7	65.9	43.2	25.0
US FDA	97.7	75.0	47.7	25.0
ESBL-phenotype (508)				
CLSI	NA	96.1	63.2	51.2
EUCAST	NA	92.7	62.2	47.8
USCAST	99.4	82.3	62.2	47.8
US FDA	98.6	96.1	63.2	51.2
MDR (298)				
CLSI	NA	92.6	39.3	18.1
EUCAST	NA	86.9	36.9	14.1
USCAST	97.7	70.1	36.9	14.1
US FDA	93.3	92.6	39.3	18.1
XDR (42)				
CLSI	NA	73.8	28.6	2.4
EUCAST	NA	66.7	23.8	0.0
USCAST	97.6	59.5	23.8	0.0
US FDA	92.9	73.8	28.6	2.4

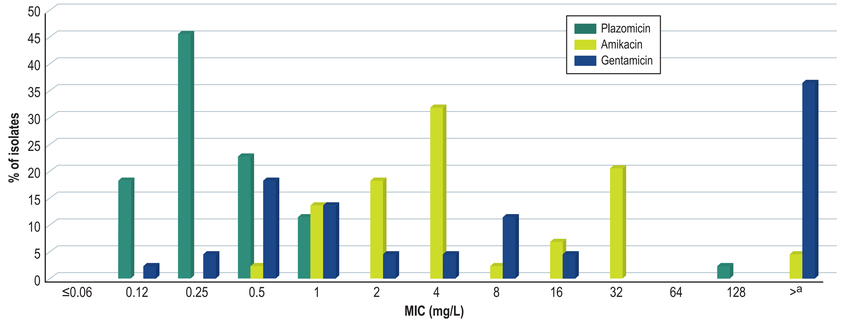
Abbreviations: CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; USCAST, United States Committee on Antimicrobial Susceptibility Testing; NA, not available; CRE, carbapenem-resistant *Enterobacterales*; ESBL, extended-spectrum β-lactamase; MDR, multidrug-resistant; XDR, extensively drug-resistant.

Figure 1 MIC distributions for plazomicin, amikacin, and gentamicin when testing *Enterobacterales* isolates from US medical centers (2018–2019)



[a] ">" indicates greater than the highest dilution tested, which was 128 mg/L for plazomicin, 32 mg/L for amikacin, and 16 mg/L for gentamicin.

Figure 2 MIC distributions for plazomicin, amikacin, and gentamicin when testing carbapenem-resistant *Enterobacterales* (CRE) isolates from US medical centers (2018–2019)



[a] ">" indicates greater than the highest dilution tested, which was 128 mg/L for plazomicin, 32 mg/L for amikacin, and 16 mg/L for gentamicin.

Figure 3 Comparison of plazomicin and amikacin susceptibility rates when applying US FDA/CLSI and USCAST criteria (US isolates, 2018–2019)

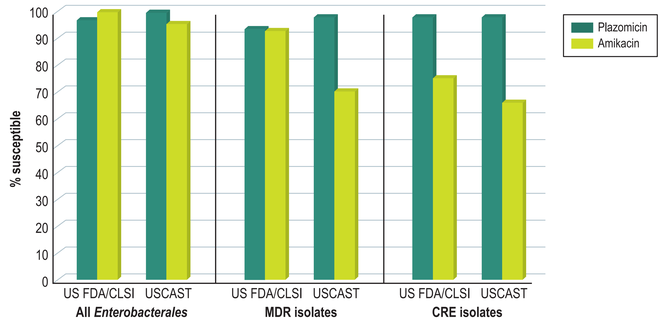


Table 2 Susceptibility rates for aminoglycosides against a worldwide collection of *Enterobacterales* isolates applying different breakpoint criteria (2018–2019)

Breakpoint setting organization/organism group (number tested)	% Susceptible			
	Plazomicin	Amikacin	Gentamicin	Tobramycin
Susceptibility breakpoints (mg/L)				
CLSI	NA	≤16	≤4	≤4
EUCAST	NA	≤8	≤2	≤2
USCAST	≤4	≤4	≤2	≤2
US FDA	≤2	≤16	≤4	≤4
Percent susceptible				
All *Enterobacterales* (9,303)				
CLSI	NA	97.4	86.4	83.8
EUCAST	NA	95.5	85.6	81.1
USCAST	98.0	90.2	85.6	81.1
US FDA	95.5	97.4	86.4	83.8
CRE (403)				
CLSI	NA	58.3	42.2	17.4
EUCAST	NA	45.7	40.4	14.6
USCAST	72.2	38.5	40.4	14.6
US FDA	71.5	58.3	42.2	17.4
ESBL-phenotype (1,907)				
CLSI	NA	88.7	52.7	38.7
EUCAST	NA	82.6	81.8	35.0
USCAST	92.7	72.4	81.8	35.0
US FDA	91.7	88.7	52.7	38.7
MDR (1,348)				
CLSI	NA	82.5	35.8	15.1
EUCAST	NA	73.5	34.3	10.9
USCAST	88.6	59.6	34.3	10.9
US FDA	86.2	82.5	35.8	15.1
XDR (365)				
CLSI	NA	55.3	33.2	2.5
EUCAST	NA	41.1	31.5	1.4
USCAST	69.9	31.2	31.5	1.4
US FDA	68.3	55.3	33.2	2.5

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; USCAST, United States Committee on Antimicrobial Susceptibility Testing; NA, not available; CRE, carbapenem-resistant *Enterobacterales*; ESBL, extended-spectrum β-lactamase; MDR, multidrug-resistant; XDR, extensively drug-resistant.

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