IDWEEK 2021

Antimicrobial Activity of Plazomicin against Multidrug-resistant *Enterobacterales*: Results from 3 Years of Surveillance in Hospitals in the United States (2018–2020)

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Introduction

- Multidrug-resistant (MDR) *Enterobacterales* isolates have increased and remain elevated in many US hospitals.
- Aminoglycoside resistance often coexists with resistance to other classes of antibiotics.
- Plazomicin is a novel, semisynthetic, parenteral aminoglycoside that was approved by the US FDA in June 2018 to treat complicated urinary tract infection (cUTI), including acute pyelonephritis.
- The US Committee on Antimicrobial Susceptibility Testing (USCAST) has lowered the breakpoints of older aminoglycosides based on contemporary pharmacokinetic/pharmacodynamic (PK/PD) parameters that were not available when these compounds first were approved and introduced to the market.
- In this study we evaluated a newer aminoglycoside, plazomicin, against a large collection of MDR *Enterobacterales* clinical isolates from US hospitals.
- We also analyzed the susceptibility rates of plazomicin, amikacin, gentamicin, and tobramycin by applying current breakpoints published by different organizations, including breakpoints generated with the same scientific rigor that was employed by regulatory agencies to evaluate the plazomicin MIC breakpoints.

Materials and Methods

- A total of 456 MDR isolates (1/patient) were collected from 32 US medical centers located in 23 states in 2018–2020.
- MDR was defined as nonsusceptible (NS) to ≥3 antimicrobial classes and extensively drug-resistant (XDR) as susceptible (S) to ≤2 classes.
- Isolates were susceptibility tested by the broth microdilution method at a monitoring laboratory (JMI Laboratories).
- Plazomicin-susceptible/resistant breakpoints published by the US FDA (≤2/≥8 mg/L) and USCAST (≤4/≥8 mg/L) were applied. Breakpoints established by the US FDA, CLSI, EUCAST, and USCAST were applied to other aminoglycosides for comparison.
- Isolates resistant to aminoglycosides and/or broad-spectrum cephalosporins were screened for aminoglycoside-modifying enzymes (AME), 16S rRNA methyltransferases, and β-lactamases by whole genome sequencing.

Results

- Plazomicin inhibited 93.0% of the MDR isolates ($MIC_{50/90}$, 0.5/1 mg/L) at the US FDA susceptible breakpoint of ≤2 mg/L and showed MIC values 8- to 16-fold lower than amikacin ($MIC_{50/90}$, 4/16 mg/L; 93.2% susceptible [S] per US FDA and CLSI; Table 1).
- Amikacin susceptibility rates were 84.6% and 69.3% when EUCAST (≤8 mg/L) and USCAST (≤4 mg/L; Table 1 and Figure 1) breakpoints were applied, respectively.
- Among agents from other classes, susceptibility rates per US FDA and/or CLSI were 85.5% for meropenem, 88.4% for tigecycline, 49.3% for piperacillin-tazobactam, and 17.8% for cefepime; only the carbapenems and tigecycline were active against >50% of MDR isolates (Table 1).
- Current aminoglycoside breakpoints published by US FDA, CLSI, and USCAST are shown in Table 2.
- The discrepancies between susceptibility rates for plazomicin and other aminoglycosides were greater when applying breakpoints generated using the same stringent contemporary methods applied to determine plazomicin breakpoints (Figures 1 and 2).
- Plazomicin showed markedly greater activity and higher susceptibility rates than amikacin per US FDA criteria against isolates classified as XDR (93.3% vs. 71.7%), AME producers (97.6% vs. 90.2%), and carbapenemase (CPE) producers (98.1% vs. 67.9%; Figures 2 and 3).

- Among the AMEs detected, *aac(6')-Ib-cr* (n=184; 40.4% of MDR) and *aac(3)-IIa* (n=167; 36.6% of MDR) were most prevalent alone or in combination with other AMEs. These AMEs were found mostly among *E. coli* and *K. pneumoniae*, and 136 isolates (29.8% of MDR) had both *aac(6')-Ib-cr* and *aac(3)-IIa* (data not shown).
- Plazomicin retained activity against isolates nonsusceptible to amikacin (83.9%S as per US FDA criteria), gentamicin (89.3%S [US FDA]), and/or tobramycin (92.4%S [US FDA]; Figure 4).
- Plazomicin was active against 99.0% of ESBL producers, while amikacin susceptibility rates were 96.2% per US FDA/CLSI (Figure 3) and only 66.2% per USCAST against these organisms.
- Plazomicin and amikacin showed similar susceptibility rates when tested against gentamicin-nonsusceptible isolates (Figure 4).
- Gentamicin and tobramycin exhibited limited activity against MDR and all resistant subsets (Table 1 and Figures 1 to 4).

Conclusions

- Despite co-resistance to aminoglycosides and other classes of antibiotics observed with MDR *Enterobacterales* isolates, plazomicin remained highly active against these isolates, including the AME, ESBL, and/or CPE producers that cause infections in US hospitals.
- Plazomicin was markedly more active than amikacin, gentamicin, or tobramycin against carbapenem-resistant *Enterobacterales* and retained good activity against isolates nonsusceptible to these old aminoglycosides.
- Susceptibility rates for amikacin, gentamicin, and tobramycin against MDR and other resistant subsets were much lower when applying interpretative criteria established with similar PK/PD parameters to those used to determine plazomicin breakpoints compared to current US FDA and CLSI breakpoints.
- Using the same stringent contemporary methods that were applied to determine plazomicin breakpoints to the older aminoglycosides can ensure consistency when evaluating the aminoglycosides.

Acknowledgements

This study was performed by JMI Laboratories and supported by Cipla Ltd, which included funding for preparing this poster.

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Table 1. Activity of plazomicin and comparator antimicrobial agents tested against 456 multidrug-resistant (MDR) *Enterobacterales* isolates from US medical centers in 2018–2020

Antimicrobial agent	mg/L		CLSI[a]		USCAST[a]	
	MIC_{50}	MIC_{90}	%S	%R	%S	%R
Plazomicin	0.5	1	93.0 [b]	3.1 [b]	96.9	3.1
Amikacin	4	16	93.2	1.8	69.3	30.7
Gentamicin	>16	>16	38.4	55.3	36.2	63.8
Tobramycin	16	>16	19.1	57.9	14.5	85.5
Cefepime	>32	>32	17.8 [c]	70.6 [c]	17.8	70.6
Ceftazidime	32	>32	13.6	77.9	13.6	77.9
Ceftriaxone	>8	>8	8.1	89.3	8.1 [c]	89.3
Imipenem	≤0.12	4	81.8	12.9	87.1	12.9
Meropenem	0.03	4	85.5	11.6	88.4	5.0
Piperacillin-tazobactam	32	>128	49.3	28.9	49.3	28.9
Levofloxacin	8	32	7.7	81.8	7.7	81.8
Tigecycline	0.5	4	88.4 [b]	2.0 [b]	77.2	11.6
Colistin	0.25	>8		12.6	87.4	12.6

[a] Criteria as published by CLSI (2021) and USCAST (2021).
[b] US FDA breakpoints were applied.
[c] Intermediate is interpreted as susceptible-dose dependent.

Table 2. Aminoglycoside breakpoints published by US FDA, CLSI, EUCAST, and USCAST

Antimicrobial	Breakpoint (susceptible/resistant) in mg/L			
	US FDA	CLSI	EUCAST	USCAST
Plazomicin	≤2 / ≥8	NA	NA	≤4 / ≥8
Amikacin	≤16 / ≥64	≤16 / ≥64	≤8 / ≥16	≤4 / ≥8
Gentamicin	≤4 / ≥16	≤4 / ≥16	≤2 / ≥4	≤2 / ≥4
Tobramycin	≤4 / ≥16	≤4 / ≥16	≤2 / ≥4	≤2 / ≥4

Figure 1. Susceptibility rates for plazomicin and comparator aminoglycosides when applying US FDA and USCAST breakpoints against 456 multidrug-resistant (MDR) *Enterobacterales* isolates from US medical centers in 2018–2020

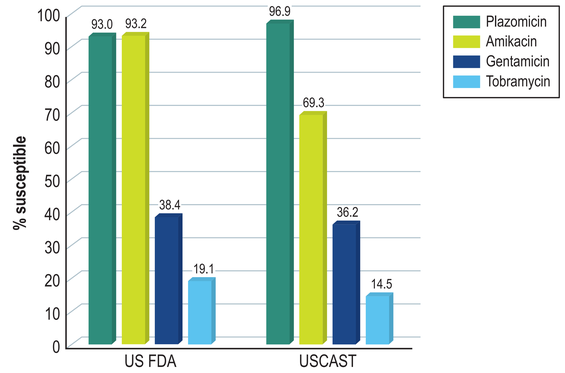


Figure 2. Susceptibility rates for plazomicin and comparator aminoglycosides when applying US FDA and USCAST breakpoints against 60 extensively drug-resistant (XDR) *Enterobacterales* isolates from US medical centers in 2018–2020

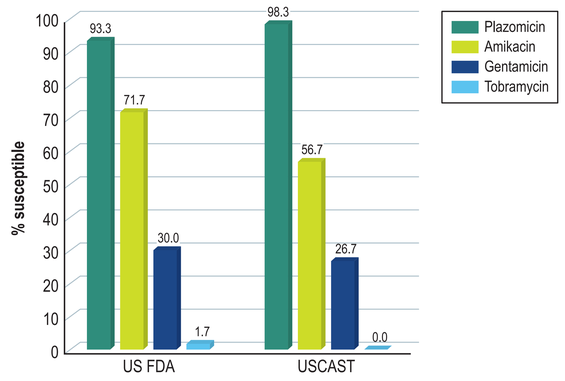
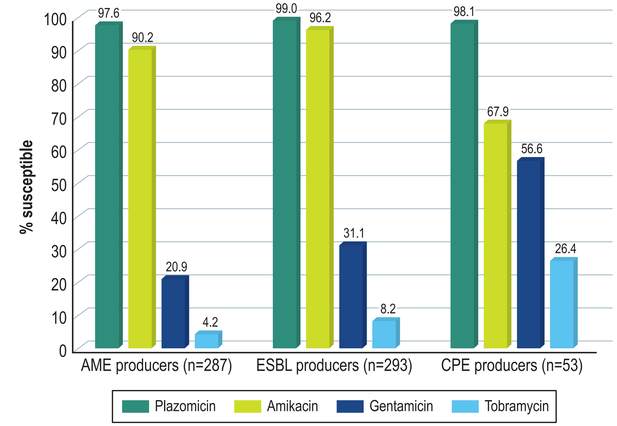
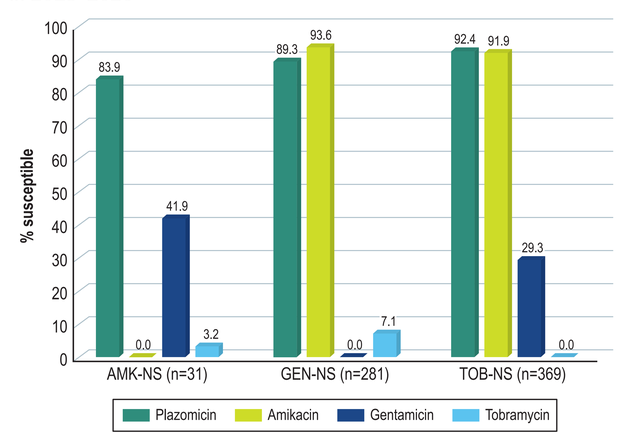


Figure 3. Susceptibility rates per CLSI and US FDA for plazomicin and comparator aminoglycosides against resistant subsets of *Enterobacterales* isolates from US medical centers in 2018–2020



Abbreviations: AME, aminoglycoside-modifying enzymes; ESBL, extended-spectrum β-lactamases; CPE, carbapenemase.

Figure 4. Susceptibility rates per CLSI and US FDA for plazomicin and comparator aminoglycosides against *Enterobacterales* isolates with decreased susceptibility to aminoglycosides from US medical centers in 2018–2020



Abbreviations: AMK, amikacin; NS, nonsusceptible; GEN, gentamicin; TOB, tobramycin.

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