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Five-Year Trends on the Susceptibility of *Enterobacterales* to Plazomicin and Other Aminoglycosides in Hospitals in the United States (2016–2020)

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Introduction

- Plazomicin is a novel semisynthetic parenteral aminoglycoside 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) established the breakpoints for older aminoglycosides based on contemporary pharmacokinetic/pharmacodynamic (PK/PD) parameters that were not available when these compounds were first approved and introduced to the market.
- Plazomicin breakpoints were established by the US FDA based on contemporary PK/PD parameters and clinical outcomes.
- In this study, we evaluated the following:
  - Plazomicin activity against clinical isolates of *Enterobacterales* from US hospitals.
  - Susceptibility rates of plazomicin, amikacin, gentamicin, and tobramycin by applying the 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 10,008 *Enterobacterales* isolates (one per patient) were collected from 35 US medical centers in 2016–2020.
- Isolates were collected from patients with cUTI (37.7%), bloodstream infection (24.9%), pneumonia (20.3%), intraabdominal infection (8.0%), skin and skin structure infection (7.6%), and other infection types (1.6%).
- 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 those published by USCAST (≤4/≥8 mg/L) were applied.
- For comparison, breakpoints established by the US FDA, CLSI, EUCAST, and USCAST were applied to the other aminoglycosides.

Results

- Plazomicin exhibited potent activity against *Enterobacterales* ($MIC_{50/90}$, 0.5/1 mg/L), with susceptibility rates varying from 97.8% in 2016 to 95.8% in 2020 (96.8% overall) as per US FDA breakpoint criteria (Table 1 and Figure 1).
- Against carbapenem-resistant *Enterobacterales* (CRE), susceptibility rates (US FDA and/or CLSI) for plazomicin increased from 96.3% in 2016 to 100.0% in 2020 (97.3% overall) and were markedly higher than amikacin (75.2% overall), gentamicin (48.7%), and tobramycin (23.0%; Table 1 and Figure 2).
- Current aminoglycoside breakpoints published by the US FDA, CLSI, EUCAST, and USCAST are shown in Table 2.
- The differences between the susceptibility rates for plazomicin and other aminoglycosides were greater when applying breakpoints generated using the same stringent contemporary methods used to determine plazomicin breakpoints (Table 3).
- CRE susceptibility rates for amikacin were 62.8% as per EUCAST (Table 1) and 52.2% as per USCAST (Table 3).
- Plazomicin retained activity against gentamicin-nonsusceptible (n=875; 90.6%/95.7% susceptible [S] as per US FDA/USCAST), tobramycin-nonsusceptible (n=944; 92.7%/96.3%S per US FDA/USCAST), and amikacin-nonsusceptible (n=60; 83.3%/85.0%S per US FDA/USCAST) isolates (Table 3).
- Among isolates from cUTI (n=3,774), 96.9% were plazomicin-susceptible, varying from 97.8% in 2017 to 95.8% in 2020 (data not shown).
- The *Enterobacterales* species most susceptible to plazomicin (lowest MIC values) were *C. koseri* (100.0%S), *K. aerogenes* (100.0%S), *K. pneumoniae* (99.8%S), and *E. cloacae* (99.7%S), all with $MIC_{50/90}$ values of 0.25/0.5 mg/L, followed by *K. oxytoca* ($MIC_{50/90}$, 0.5/0.5 mg/L; 99.9%S), *E. coli* ($MIC_{50/90}$, 0.5/1 mg/L; 99.6%S), and *C. freundii* ($MIC_{50/90}$, 0.5/1 mg/L; 100.0%S; data not shown).

Conclusions

- Plazomicin demonstrated potent activity (with 4-fold lower MIC values than amikacin) against a large collection of contemporary *Enterobacterales* isolates from US hospitals.
- Plazomicin was markedly more active than amikacin, gentamicin, or tobramycin against CRE and retained good activity against isolates nonsusceptible to these aminoglycosides.
- When applying interpretative criteria established with similar PK/PD parameters to those used to determine plazomicin breakpoints, the activities of amikacin, gentamicin, and tobramycin were found to be much lower, especially against CRE.

Acknowledgements

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Figure 1. Yearly susceptibility rates for plazomicin compared to other aminoglycosides (as per US FDA criteria) against *Enterobacterales* from US hospitals (2016–2020)

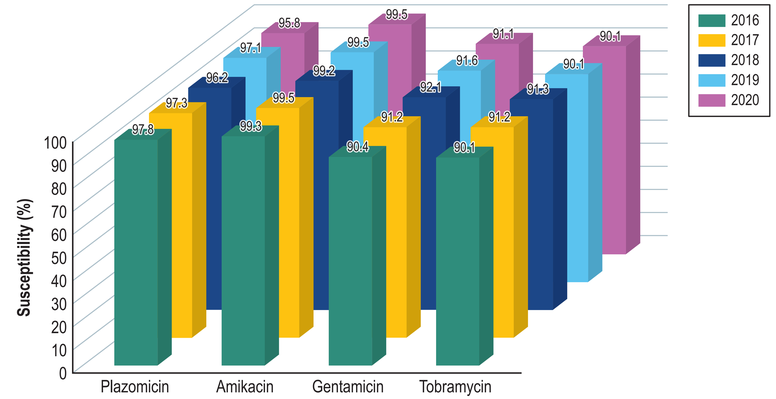

Figure 2. Yearly susceptibility rates for plazomicin compared to other aminoglycosides (as per US FDA criteria) for the aminoglycosides against CRE from US hospitals (2016–2020)

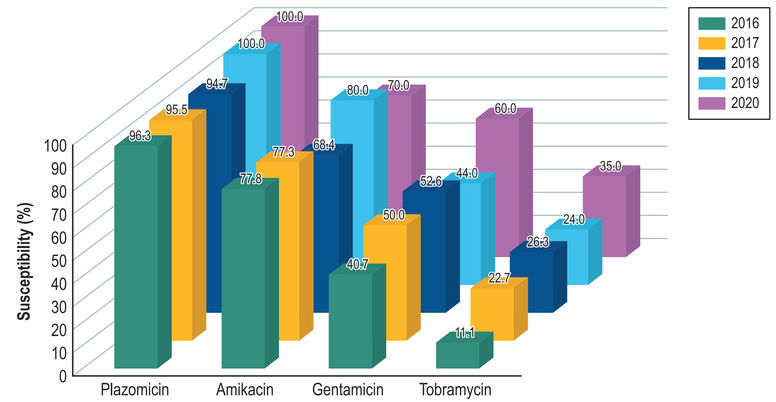

Table 1. Activity of plazomicin and comparator antimicrobial agents tested against *Enterobacterales* isolates from US medical centers in 2016–2020

Antimicrobial agent	mg/L		CLSI / US FDA[a]		USCAST[a]	
	MIC_{50}	MIC_{90}	%S	%R	%S	%R
Enterobacterales (10,008)						
Plazomicin	0.5	1	96.8 [b]	0.7 [b]	99.3	0.7
Amikacin	2	4	99.4	0.2	95.0	5.0
Gentamicin	0.5	2	91.3	7.8	90.5	9.5
Tobramycin	0.5	4	90.6	6.1	87.9	12.1
Ceftriaxone	≤0.06	>8	82.8	16.3	82.8	16.3
Imipenem	≤0.12	1	92.5	2.1	97.9	2.1
Meropenem	0.03	0.06	98.8	1.0	99.0	0.8
Piperacillin-tazobactam	2	16	92.2	4.6	92.2	4.6
Levofloxacin	0.06	>4	79.7	17.0	79.7	17.0
Colistin	0.25	>8		15.3	84.7	15.3
CRE[c] (113)						
Plazomicin	0.25	1	97.3 [b]	1.8 [b]	98.2	1.8
Amikacin	4	32	75.2	7.1	52.2	47.8
Gentamicin	8	>8	48.7	39.8	45.1	54.9
Tobramycin	>8	>8	23.0	68.1	22.1	77.9
Imipenem	8	>8	7.1	90.3	9.7	90.3
Meropenem	8	>32	3.5	87.6	12.4	70.8
Levofloxacin	>4	>4	14.2	82.3	14.2	82.3
Colistin	0.12	0.5		8.9	91.1	8.9

[a] Criteria as published by CLSI (2021) and the US Committee on Antimicrobial Susceptibility Testing (USCAST; 2021).
[b] US FDA breakpoints were applied.
[c] CRE, carbapenem-resistant *Enterobacterales*.

Table 2. Aminoglycoside's breakpoints published by the 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

Table 3. Antimicrobial activity of aminoglycosides against *Enterobacterales*-resistant subsets when applying breakpoints generated using the same stringent, contemporary methods applied to determine plazomicin breakpoints

Antimicrobial	% Susceptible as per US FDA / USCAST criteria (no. of isolates)					
	All (10,008)	CRE[a] (113)	CRO-R[a] (1,635)	AMK-NS[a] (60)	GEN-NS[a] (875)	TOB-NS[a] (944)
Plazomicin	96.8 / 99.3	97.3 / 98.2	97.9 / 99.1	83.3 / 85.0	90.6 / 95.7	92.7 / 96.3
Amikacin	99.4 / 95.0	75.2 / 52.2	96.8 / 84.2	0.0 / 0.0	97.0 / 80.9	93.9 / 69.0
Gentamicin	91.3 / 90.5	48.7 / 45.1	67.5 / 66.0	56.7 / 51.7	0.0 / 0.0	24.6 / 22.1
Tobramycin	90.6 / 87.9	23.0 / 22.1	58.4 / 54.4	3.3 / 1.7	18.6 / 4.6	0.0 / 0.0

[a] Resistant subsets were selected based on US FDA/CLSI breakpoint criteria.
Abbreviations: CRE, carbapenem-resistant *Enterobacterales*; CRO, ceftriaxone; R, resistant; AMK, amikacin; NS, nonsusceptible; GEN, gentamicin; TOB, tobramycin.