

Comparison of Plazomicin MIC Test Strip and Broth Microdilution MIC Results for 125 Enterobacteriaceae

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Abstract (updated)

Background: Plazomicin (PLZ) is a next-generation aminoglycoside with in vitro activity against MDR Enterobacteriaceae, including CRE. PLZ has been approved by the FDA for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis caused by the following susceptible microorganism(s): *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Enterobacter cloacae*. This study was performed to evaluate the performance of a newly developed gradient strip, the plazomicin MIC Test Strip (MTS) from Liofilchem, Waltham, MA compared to the broth microdilution method against relevant Enterobacteriaceae.

Methods: The study isolates included 125 Enterobacteriaceae (12 species as shown in the table), which were chosen to include a range of plazomicin MICs and isolates with known resistant mechanisms. Each isolate was tested for PLZ MIC by broth microdilution (BMD); LSI prepared frozen panels) and by PLZ MTS on 100 mm Mueller Hinton agar (MHA) plates (Becton Dickinson, Sparks, MD) and a subset of 20 strains was also tested on MHA plates from two additional manufacturers (Hardy, Santa Maria, CA and Remel, Lenexa, KA). Quality control (QC) strains (*E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853) were tested on each day of testing and results compared to CLSI expected ranges.

Results: As shown in the Table 1, PLZ MTS and BMD results were within +/- one doubling dilution (essential agreement) for 99.2% of all study isolates. The category agreement rate was 91.2% (based on proposed susceptible/intermediate/resistant breakpoints of $\leq 4/8/\geq 16$ $\mu\text{g/mL}$). The QC results were within CLSI published ranges. PLZ results for MTS tested on Remel and Hardy MHA for the subset of 20 isolates were similar to BD MHA results (equivalent or 1 dilution lower).

Table: Comparison of Plazomicin MTS to BMD for all study isolates (Dilution Difference of MTS MIC compared to BMD MIC)

Organism	Dilution Difference by				
	-2	-1	0	1	2
Citrobacter spp.			1	4	
Enterobacter aerogenes		1	3	1	
Enterobacter cloacae		1	8	11	
Escherichia coli		4	14	3	
Klebsiella oxytoca			4	2	
Klebsiella pneumoniae		1	11	9	
Morganella morganii	1	2			
Proteus mirabilis		4	13	2	
Proteus vulgaris			3	12	
Providencia rettgeri		1	1	1	
Serratia marcescens			4	1	

Conclusions:
This initial evaluation of the plazomicin MTS showed good correlation to BMD MIC. Further testing with additional isolates and media at multiple test sites was warranted.

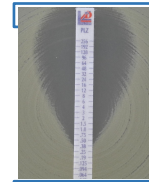
Methods

Study Isolates

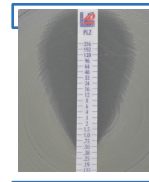
The study isolates were selected to include a range of plazomicin MIC results, including susceptible and non-susceptible isolates. Among the study isolates were 40 molecularly characterized strains, which included 25 carbapenemase producing strains.

Organism	n
<i>Citrobacter freundii</i>	3
<i>Citrobacter koseri</i>	2
<i>Enterobacter aerogenes</i>	5
<i>Enterobacter cloacae</i>	20
<i>Escherichia coli</i>	21
<i>Klebsiella oxytoca</i>	6
<i>Klebsiella pneumoniae</i>	21
<i>Morganella morganii</i>	5
<i>Proteus mirabilis</i>	19
<i>Proteus vulgaris</i>	15
<i>Providencia rettgeri</i>	3
<i>Serratia marcescens</i>	5

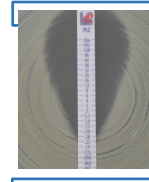
QC Organism	CLSI Expected QC Range
<i>E. coli</i> ATCC 25922	0.25-2 $\mu\text{g/mL}$
<i>P. aeruginosa</i> ATCC 27853	1-4 $\mu\text{g/mL}$



E. coli
Plazomicin MIC = 0.38 $\mu\text{g/mL}$, reported as 0.5 $\mu\text{g/mL}$.



E. cloacae
Plazomicin MIC = 0.5 $\mu\text{g/mL}$.



K. pneumoniae
Plazomicin MIC = 0.38 $\mu\text{g/mL}$, reported as 0.5 $\mu\text{g/mL}$.

Results

Quality Control (Table 1): All plazomicin BMD and MTS MIC results were within CLSI expected QC ranges. For *P. aeruginosa* ATCC 27853, 70% of MTS results (BD MHA) were 4 $\mu\text{g/mL}$ (upper end of the expected range).

Plazomicin (BD MHA) compared to BMD:

125 Enterobacteriaceae (Figure 1): MTS were within +/- one dilution of BMD results for 100% of isolates. 12.8% categorical error rate was attributed to minor errors. Among 26 isolates that were resistant by BMD, 22 were resistant and 4 were intermediate by MTS. Trending of one dilution higher MTS MIC results was observed for strains with BMD MIC results of 0.25 and 0.5 $\mu\text{g/mL}$ (48.8% of 41 strains were one dilution higher by MTS).

25 genetically characterized carbapenemase-producing Enterobacteriaceae (Figure 2): MTS were within +/- one dilution of BMD results for 100% of isolates. 4.0% categorical error rate was attributed to minor errors.

Plazomicin MTS (Hardy and Remel MHA) subset of 70 isolates compared to MTS (BD MHA) (Table 2):

Hardy MHA: Hardy MHA results were within ± 1 dilution of BD MHA results for 100% of isolates. Hardy MHA results were 1 dilution lower compared to BD MHA results for 6/20 and equivalent for 14/20 isolates.

Remel MHA: Remel MHA results were within ± 1 dilution of BD MHA results for 100% of isolates. Remel MHA results were 1 dilution lower compared to BD MHA results for 6/20 and equivalent for 13/20 isolates.

References:

- Clinical and Laboratory Standards Institute. 2015. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, 10th ed. Approved standard, CLSI M7-10, Wayne, PA.
- Clinical and Laboratory Standards Institute. 2017. Performance Standards for Antimicrobial Susceptibility Testing. Approved Standard – 27th Edition. CLSI document M100-27. Wayne, PA.
- http://www.liofilchem.net/en/mov_mic_test_strip.php

Figure 1. Plazomicin MTS MIC compared to BMD MIC for 125 Enterobacteriaceae (number of results at each MIC)

MTS MIC Results ($\mu\text{g/mL}$)	BMD MIC Results ($\mu\text{g/mL}$)															
	<0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	>256
<0.016																
0.03																
0.06																
0.12																
0.25						1	4									
0.5							15	17	2							
1								5	17	3						
2									4	12	5					
4										4	7	4				
8											3	10	2	1		
16												1	8	1		
32																
64																
128																
256																
>256															1	4

Evaluation	
Overall Essential Agreement (EA)	126 / 126 100%
EA based on evaluable results	119 / 120 99.2%
Category agreement based on interpretation	106 / 125 87.2%
Category Minor Errors	16 / 125 12.8%
Agreement Major Errors	0 / 24 0.0%
Very Major Errors	0 / 26 0.0%

Figure 2. Plazomicin MTS MIC compared to BMD MIC for a subset of 25 genetically characterized carbapenemase-producing Enterobacteriaceae (number of results at each MIC)

MTS MIC Results ($\mu\text{g/mL}$)	BMD MIC Results ($\mu\text{g/mL}$)															
	<0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	>256
<0.016																
0.03																
0.06																
0.12																
0.25						1										
0.5							8	4	1							
1								1	2	1						
2										1						
4											1					
8																
16																
32																
64																
128																
256																
>256																3

Evaluation	
Overall Essential Agreement (EA)	25 / 25 100.0%
EA based on evaluable results	22 / 22 100.0%
Category agreement based on interpretation	24 / 24 100.0%
Category Minor Errors	1 / 24 4.0%
Agreement Major Errors	0 / 19 0.0%
Very Major Errors	0 / 2 0.0%

Table 1: Quality Control Results

MIC Method	MHA	QC Organism	Plazomicin MIC ($\mu\text{g/mL}$)			
			0.25	0.5	1	2
MTS	BD	<i>E. coli</i> ATCC 25922		19	1	
MTS	Remel	<i>E. coli</i> ATCC 25922		1	1	
MTS	Hardy	<i>E. coli</i> ATCC 25922		2		
BMD	BD	<i>P. aeruginosa</i> ATCC 27853		2	5	
MTS	BD	<i>P. aeruginosa</i> ATCC 27853				6 14
MTS	Remel	<i>P. aeruginosa</i> ATCC 27853				2
MTS	Hardy	<i>P. aeruginosa</i> ATCC 27853				2
BMD	BD	<i>P. aeruginosa</i> ATCC 27853		4	2	

Table 2: Comparison of Plazomicin MTS MIC results on Hardy and Remel MHA compared to BD MHA for 20 strains

MHA	Dilution Difference by			
	-2	-1	0	1
Hardy	6	14		
Remel	6	13	1	

Conclusions

- Overall there was good correlation of plazomicin MTS MIC results to BMD MIC results.
- MTS accurately detected resistance (or intermediate resistance) among the 26 isolates that were considered resistant by BMD.
- Since the completion of this study, a multi-lab 510(k)-based study was performed and FDA clearance obtained



Poster PDF