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

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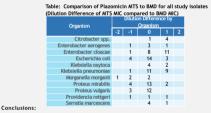
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Abstract (updated)

Background: Plazomicin (PLZ) is a next-generation aminoglycoside with in vitro activity against MDR Enterobactericeae, including CRE. PLZ has been approved by the FDA for the treatment of complicated urinary tract infections (cUTI), including psyclonephritis 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 Liofitchem, Waitham, 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 (BMU; LSJ prepared frozen panels) and by PLZ MTS on 100 mm Mueller Hinton agar (MHA) plates (from two additional manufacturers (Hardy, Santa Maria, CA and Remel, Lenexa, KA). Quality control (QC) strains (E. coil XTCC 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 s4/8/16 μ 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).



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.

Introduction

- Plazomicin is an aminoglycoside that acts by binding to bacterial 305 ribosomal subunit, thereby inhibiting protein synthesis. The in vitro activity of plazomicin has been demonstrated against Enterobacteriaceae in the presence of certain beta-lactamases, including extended-spectrum 6lactamases (TeM, SHY, CTX-M, AmpC), serior carbapenemases (RPC2, RPC-3), oaxaillinase (OXA-48) and metallo-6-lactamases (VIM, IMR, NDM). Plazomicin is not active against isolates that express 165 rRNA methyltransferase, which are sometimes co-expressed with metallo-6-lactamases.
- Liofilchem manufactures MIC test strips (MTS) for a variety of antimicrobial agents. The Liofilchem MIC test strip is a quantitative agar-based diffusion assay for determining the minimum inhibitory concentration (MIC).
- This study was performed as part of a preliminary evaluation of the plazomicin MTS strip, prior to initiating a U.S. 510(k) study. Since the submission of this abstract, a 510(k) study for plazomicin MTS was performed and was submitted and cleared by FDA.
- This study compared the plazomicin MTS MIC to broth microdilution MIC for the clinically indicated cUTI Enterobacteriaceae species and for those additional species with recognized in vitro activity.

Nethods						
	Organism	n				
Study Isolates	Citrobacter freundii	3				
The study isolates were	Citrobacter koseri	2		CLSI Expected		
selected to include a range	Enterobacter aerogenes	5	QC Organism	QC Range		
of plazomicin MIC results, including susceptible and	Enterobacter cloacae	20	E coli	-		
	Escherichia coli	21	ATCC 25922	0.25-2 µg/mL		
non-susceptible isolates. Among the study isolates	Klebsiella oxytoca	6				
were 40 molecularly	Klebsiella pneumoniae	21	P. aeruginosa			
characterized strains, which	Morganella morganii	5	ATCC 27853	1-4 µg/mL		
included 25 carbapenemase	Proteus mirabilis	19				
producing strains.	Proteus vulgaris	15				
	Providencia rettgeri	3				
	Serratia marcescens	5				

Testing site: Laboratory Specialists, Inc., Westlake, OH

MIC methods:

N

- * All isolates were tested once by broth microdilution (BWD) according to CLSI method (1) and once by MTS on Bection Dickinson MHA (Sparks, MD) uning the same initial suspension (equivalent to 0.5 McFarland standard) for both methods. A subset of 20 Enterobacteriaceae (1 C, freundii, 1 E, aerogenes, 2 E, cloacea, e E, coli, 1 K. oxytoca, 5 K, preumonie, 1 M. morganii, 2 P. mirabilis, 2 P. wigaris, 1 S. marcesens and 4 P. aeruginosa) 2 (Oc strains were tested by MTS on 2 additional commercial media lots (Hardy) (Stant Awais, CA) and Reme [Lenexa, KS])
- Quality control strains (E. coli ATCC 25922 and P. aeruginosa ATCC 27853) were tested each day of testing.
- MTS results were rounded up to next doubling dilution for analysis. MIC results were interpreted according to the approved FDA breakpoints.

Results

- <u>Quality Control (Table 1)</u>; 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 µe/mi (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 0.025 and 0.5 gp/m1 (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 20 isolates compared to MTS (BD MHAL (Table 2):

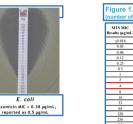
Hardy MHA: Hardy MHA results were within ± 1 dilution of BD MHA results for 100% of isolates. Hardy MHA results were 1 dilution lower compared to BD MHA results for 6/20 and equivalent for 14/20 isolates.

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 27h Edition. CLSI document M100-27 Wayne, PA
- 3. http://www.liofilchem.net/en/mov_mic_test_strip.php







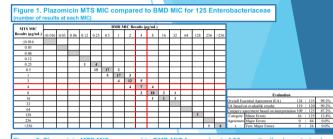


Figure 2. Plazomicin MTS MIC compared to BMD MIC for a subset of 25 genetically characterized carbapenemase-producing Enterobacteriaceae (number of results at each MIC)

							g/mL)	sults (p	IIC Re	BMD N	1						MTS MIC
	>256	256 >256	128	64	32	16	8	4	2	1	0.5	0.25	0.12	0.06	0.03	⊴0.016	Results (µg/mL)
																	⊴0.016
																	0.03
																	0.06
																	0.12
												1					0.25
										1	4	8					0.5
Evaluation									1	2	1						1
sential Agreement (EA) 25 / 25 100								1		1							2
on evaluable results 22 / 22 100								1									4
greement based on interpretation 24 / 25 96.							1										8
Minor Errors 1 / 25 4.0							-										16
Major Errors 0 / 19 0.0 Very Major Errors 0 / 4 0.0	Agreeme																32
very Major Errors 0 / 4 0.0 with BMD MIC 0.25 and MTS MIC 0.5 were E. cloacae	1	-	-			-		-			-	-			-		64
with BMD MIC 0.25 and M18 MIC 0.5 were E. cloacue h BMD and MTS MIC 1 was P. mirabilis (DHA-1, IMP-				_													128
ith BMD and MTS MIC 1 was P. moreniti (DHA-1, Bar- ith BMD and MTS MIC >256 were NDM (E. coli. E								-									256
nd P. mirabilis)		3	_						-		-	-	-				>256

Table 1: Quality Control Results																
Table 1. Quality Control Results									Table	Table 2: Comparison of Plazomicin						
MIC Method	MHA	QC Organism	Plazomicin MIC (µg/mL) 0.25 0.5 1 2 4									on Hardy				
MTS	BD	E. coli ATCC 25922	19 1						MHA	MHA compared to BD MHA for 20						
MTS	Remel	E. coli ATCC 25922														
MTS	Hardy	E. coli ATCC 25922	2 strains													
BMD		E. coli ATCC 25922		2	5											
MTS	BD	P. aeruginosa ATCC 27853				6	14									
MTS	Remel	P. aeruginosa ATCC 27853					2		Hardy		6	14				
MTS	Hardy	P. aeruginosa ATCC 27853					2		Remel		6	13	1			
BMD		P. aeruginosa ATCC 27853				4	2		Remet		0	13				
		CLSI Expected Range							X							

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

K. pneumoniae

Plazomicin MIC = 0.38 µg/mL reported as 0.5 µg/mL