Performance of VITEK® 2 AST-GN Meropenem / Vaborbactam (S ≤ 4/8 µg/mL, I = 8/8 µg/mL and R ≥ 16/8 µg/mL) Compared to Broth Microdilution with *Enterobacteriaceae*

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ABSTRACT

Background: Meropenem/Vaborbactam (MEV), a β-lactam combination antimicrobial consisting of meropenem, a carbapenem, and vaborbactam, a beta-lactamase inhibitor, is indicated for treatment of patients 18 years and older with complicated urinary tract infections (cUTI) including pyelonephritis caused by designated susceptible bacteria. In this study, the performance of VITEK® 2 MEV with *Enterobacteriaceae* was evaluated against the CLSI broth microdilution (BMD) reference method.

Method: A total of 449 *Enterobacteriaceae* isolates (clinical and challenge combined) were tested by four clinical trial sites with VITEK® 2 MEV and BMD reference (CLSI M07 11th Ed.) methods. The results were analyzed for essential agreement (EA), category agreement (CA), major (ME) and very major errors (VME) rates following the FDA performance criteria (EA and CA ≥90%, ME ≤3.0% and VME ≤2.0%) and using the FDA *Enterobacteriaceae* breakpoints for MEV (S = ≤4/8 µg/mL, I = 8/8 µg/mL, R = ≥16/8 µg/mL).

Results: VITEK® 2 MEV performance results are summarized in Table 1. VITEK® 2 MEV overall performance for *Enterobacteriaceae* met the FDA performance criteria for EA, CA, ME and VME. There were no categorical major or very major errors for *Enterobacteriaceae.*

Table 1: Summary of VITEK® 2 AST GN-MEV Performance

Claimed Species	EA	CA	CA VME Rate	CA ME Rate	CA mE Rate
Enterobacteriaceae (FDA)	(441/449) 98.2%	(443/449) 98.7%	(0/33) 0.0%	(0/413) 0.0%	(6/449) 1.3%

Conclusion: When compared to the broth microdilution reference method, VITEK® 2 AST GN-MEV proved to be an accurate test for susceptibility testing of *Enterobacteriaceae* for Meropenem/Vaborbactam.

INTRODUCTION

VITEK®2 antimicrobial susceptibility test (AST) Gram-negative Meropenem/Vaborbactam (GN-MEV) is an *in vitro* quantitative test device for determining the antimicrobial susceptibility of *Enterobacteriaceae* against MEV. It determines the Minimum Inhibitory Concentration (MIC) for MEV. The VITEK®2 AST components are antimicrobials in combination with growth medium, which are incorporated into VITEK®2 card products for use with the VITEK®2 system for performing AST testing of microorganisms in clinical laboratory settings.

The VITEK®2 GN AST card consists of 64 wells. Each well contains an aliquot of a specific concentration of antimicrobial agent. Once the cards are placed in the VITEK®2 System along with the appropriate organism suspension, no additional handling is required. Dilutions (if required) are made automatically and the cards are inoculated using a vacuum filling process. The cards are then sealed and placed into the reader / incubator automatically. The VITEK®2 Compact System requires the user to manually prepare the AST dilution and transfer the AST cards between filling and loading stations. For both the VITEK®2 and VITEK®2 Compact Systems, the computer determines growth based on the attenuation of light measured by an optical scanner. The data are used to determine the MIC values for the antimicrobial agents.

OBJECTIVE

Evaluate VITEK®2 AST GN-MEV performance when used with the VITEK®2 and VITEK®2 Compact Systems in a clinical setting, and to show the equivalence of the product to the CLSI broth microdilution (BMD) technique. *Enterobacteriaceae* were evaluated for the FDA 510 (k) submission and CE marking.

MATERIALS AND METHODS

Clinical (fresh and stock), challenge, reproducibility and quality control (QC) isolates were evaluated at four clinical trial sites in the United States, three external and one internal. Each isolate was first subcultured onto TSA blood agar.

Using an 18-24 hour culture, a DensiCHEK™ Plus instrument was used to create a bacterial suspension with 0.5–0.63 McFarland range. Clinical, challenge, reproducibility, and QC isolates were tested on the VITEK®2 System with the automatic dilution option. In addition, the VITEK®2 System with manual dilution and the VITEK®2 Compact options for inoculum preparation were evaluated for challenge, reproducibility and QC strains.

One initial McFarland suspension was prepared for each isolate for inoculation of all the cards, and the reference method when applicable.

Table 2 : Sample Type and Testing Method

	Clinical	Challenge	Reproducibility	QC
1st card	VITEK®2 automatic dilution	VITEK®2 automatic dilution	VITEK®2 automatic dilution	VITEK®2 automatic dilution
2nd card	N/A	VITEK®2 manual dilution	VITEK®2 manual dilution	VITEK®2 manual dilution
3rd card	N/A	VITEK®2 Compact manual dilution	VITEK®2 Compact manual dilution	VITEK®2 Compact manual dilution
BMD	Yes	Yes	No	Yes

RESULTS

Quality Control: Six Gram-negative QC organisms were tested throughout comparative testing at each study site by both the VITEK®2 AST GN-MEV and BMD reference method containing MEV. The testing was performed a minimum of twenty times by both card and reference method at each site. Overall card and reference performance is shown in Table 3 below.

Table 3 : Quality Control

QC Strain	CLSI QC Range (Vaborbactam is fixed 8)	% Meropenem / Vaborbactam Card Results within Range			% of Reference within Range
		Auto	Manual	Compact	
Escherichia coli ATCC 25922	0.008- 0.06	(116/116) 100%	(90/90) 100%	(90/90) 100%	(116/116) 100%
Escherichia coli ATCC 35218	0.008 - 0.06	(116/116) 100%	(91/91) 100%	(91/91) 100%	(116/116) 100%
Klebsiella pneumoniae ATCC 700603	0.016 - 0.06	(115/115) 100%	(89/89) 100%	(89/89) 100%	(114/115) 99.1%
Klebsiella pneumoniae ATCC BAA-1705	0.008 - 0.06	(114/114) 100%	(89/89) 100%	(89/89) 100%	(114/114) 100%
Klebsiella pneumoniae ATCC BAA-2814	0.12 - 0.5	(115/115) 100%	(88/89) 98.9%	(89/89) 100%	(111/115) 96.5%
Pseudomonas aeruginosa ATCC 27853	0.12 - 1	(117/117) 100%	(92/92) 100%	(92/92) 100%	(117/117) 100%

Reproducibility: Ten Gram-negative organisms were selected for this study. Reproducibility data were collected at three external sites. A data summary is presented in Table 4.

Table 4 :Overall Combined Reproducibility

VITEK® 2 System(s) Card Inoculum Method	Overall Reproducibility
VITEK® 2 Automatic Dilution	97.78%
VITEK® 2 Manual Dilution	97.41%
VITEK® 2 Compact Manual Dilution	96.67%

Clinical and Challenge Performance: Twenty one species were included in the overall performance for VITEK®2 AST GN-MEV. Acceptable performance was based upon the combined clinical and challenge data. The VITEK®2 MIC value for each isolate was compared to the MIC value of the broth microdilution reference method. The overall distribution of the VITEK®2 card and BMD reference MIC value is presented in Table 5 below, while the performance summary for each species (or sub-species when applicable) is presented in Table 6.

Table 5: Clinical and Challenge Frequency Table for *Enterobacteriaceae*

Test Results	Reference															
	≤0.0039	0.0078	0.0156	0.0313	0.0625	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥256
≤0.5			93	185	56	33	17	11	1								
1								1	2	1							
2							1		1	2	3	2					
4									1	2	1						
8									1		1		1				
16													2	2			
32													1	3	6	6	2	7
≥64																1	3	
Evaluable Results						1	1		5	5	5	3	6	8	6	2		

Table 6: Clinical and Challenge Performance Summary for *Enterobacteriaceae*

Organism	Total	EA		CA					
		#	%	#	%	#R	#VME	#ME	#mE
Citrobacter braakii	1	1	100%	1	100%	0	0	0	0
Citrobacter freundii	8	8	100%	8	100%	0	0	0	0
Citrobacter koseri	5	5	100%	5	100%	0	0	0	0
Enterobacter cloacae	28	26	92.9%	27	96.4%	1	0	0	1
Enterobacter cloacae complex	22	22	100%	22	100%	0	0	0	0
Klebsiella (Enterobacter) aerogenes	40	39	97.5%	39	97.5%	0	0	0	1
Escherichia coli	107	105	98.1%	107	100%	9	0	0	0
Escherichia vulneris	2	2	100%	2	100%	0	0	0	0
Klebsiella oxytoca	24	24	100%	24	100%	1	0	0	0
Klebsiella pneum. spp. ozaenae	1	1	100%	1	100%	0	0	0	0
Klebsiella pneum. pneumoniae	11	11	100%	10	90.9%	1	0	0	1
Klebsiella pneumoniae	129	128	99.2%	127	98.4%	20	0	0	2
Lelliottia amnigena 2	1	1	100%	1	100%	0	0	0	0
Morganella morganii	10	9	90.0%	9	90.0%	0	0	0	1
Pantoea dispersa	2	2	100%	2	100%	0	0	0	0
Proteus mirabilis	25	24	96.0%	25	100%	0	0	0	0
Proteus penneri	1	1	100%	1	100%	0	0	0	0
Proteus vulgaris	1	1	100%	1	100%	0	0	0	0
Providencia rettgeri	3	3	100%	3	100%	0	0	0	0
Providencia stuartii	4	4	100%	4	100%	0	0	0	0
Raoultella ornithinolytica	1	1	100%	1	100%	0	0	0	0
Serratia fonticola	1	1	100%	1	100%	0	0	0	0
Serratia marcescens	21	21	100%	21	100%	1	0	0	0
Serratia rubidaea	1	1	100%	1	100%	0	0	0	0
All species combined	**449**	**441**	**98.2%**	**443**	**98.7%**	**33**	**0**	**0**	**6**

CONCLUSIONS

When compared to the broth microdilution reference method, VITEK®2 AST GN-MEV was found to be an accurate and reliable method for susceptibility testing of MEV providing MIC results for *Enterobacteriaceae*.

The addition of the VITEK®2 AST GN-MEV to the current VITEK®2 antimicrobial susceptibility test menu increases the options available to clinical laboratories for testing *Enterobacteriaceae*. VITEK®2 AST GN-MEV is FDA 510 (k) cleared.