ETEST® Meropenem/Vaborbactam for Antimicrobial Susceptibility testing of Enterobacterales and *Pseudomonas aeruginosa*: performance results from a multicentre study.

C. Anglade[1], S. Garrett[1], J. Richards[2], L. Davies[2], C. Burnham[3], O. B. Garner[4], M. Wootton[2], G. Zambardi[5], V. Sauvonnet[5]

[1]bioMérieux Global Clinical Affairs, Marcy-L'étoile, France. [2]University Hospital of Wales (SACU), Cardiff, UK. [3]Washington University, Saint Louis, MO. [4]University of California Los Angeles (UCLA) Medical Center, Los Angeles, CA. [5]bioMérieux, La Balme les Grottes, France.

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INTRODUCTION

Meropenem/Vaborbactam (MEV) is a combination of meropenem, a penem antibacterial, and vaborbactam, a beta-lactamase inhibitor, indicated for the treatment of the following infections in adults: complicated urinary tract infection (cUTI), including pyelonephritis, complicated intra-abdominal infection (cIAI), hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP), bacteraemia, in association with, or suspected to be associated with, any of the infections listed above and infections due to aerobic Gram negative organisms in patients with limited treatment options. This study evaluated the performance of ETEST® MEV, a new gradient diffusion strip (not yet CE marked but FDA cleared) for determining antimicrobial susceptibility of Enterobacterales and *Pseudomonas aeruginosa* as compared to ISO 20776-2 broth microdilution reference method (BMD).

MATERIAL & METHODS

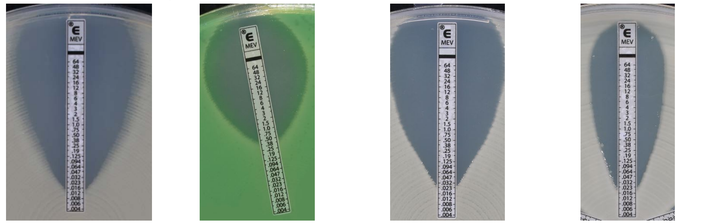
A population of 792 isolates including 629 Enterobacterales and 163 *P. aeruginosa* were tested at 4 clinical trial sites, including one internal laboratory, 2 US sites and 1 EU site.

Each isolate was subcultured twice on TSA blood agar. From the second subculture calibrated suspension was prepared in normal saline using visual comparison to MacFarland (McF) standards. 0.5 McF suspension was prepared for each isolate to inoculate a CLSI/ISO BMD panel and a Mueller Hinton agar plate for ETEST® MEV (1 McF for mucoid strains).

ETEST® MEV and BMD Minimum Inhibitory Concentration (MIC) endpoint were recorded after 16-20h incubation at 35±2°C in ambient air. For ETEST® MEV, MIC endpoint corresponded to the value where the respective inhibition ellipses intersect the strip (Figure 1 for examples). For BMD, MIC endpoint corresponded to the lowest concentration of MEV that shows complete inhibition of growth.

The results were analyzed in terms of essential (EA), category (CA) agreements, minor (mE), major (ME) and very major (VME) error rates following ISO-20776 part 2 performance criteria and using the EUCAST breakpoints for MEV (Enterobacterales: ≤8/8 (S) and >8/8 (R) mg/L, *P. aeruginosa*: ≤8/8 (S) and >8/8 (R) mg/L).

Figure 1: Characteristic elipses observed with QC strains.



E. coli
ATCC® 25922™
MIC = 0.016 µg/ml

P. aeruginosa
ATCC® 27853™
MIC = 0.5 µg/ml

K. pneumoniae
ATCC® 700603™
MIC = 0.032 µg/ml

K. pneumoniae
ATCC® BAA-1705™
MIC = 0.023 µg/ml

RESULTS & DISCUSSION

Overall performance is detailed in Table 1 and the performance of Enterobacterales per species is summarized in Table 2.

Organisms	EA	CA	ME rate	VME rate
Enterobacterales (excluding *P. mirabilis*)	**95.8%** (569/594)	**99.7%** (592/594)	**0.0%** (0/582)	**16.7%** (2/12)
P. aeruginosa	**93.3%** (152/163)	**97.5%** (159/163)	**2.7%** (4/147)	**0.0%** (0/16)

Table 1: Overall performances of ETEST® MEV

Organisms	%EA	%CA	# R	# ME	# VME
C. freundii	96.9% (31/32)	100.0% (32/32)	0	0	NA
C. koseri	96.9% (31/32)	100.0% (32/32)	0	0	NA
K. aerogenes	93.9% (31/33)	100.0% (33/33)	0	0	NA
E. cloacae	100.0% (21/21)	100.0% (21/21)	0	0	NA
E. cloacae complex	100.0% (77/77)	100.0% (77/77)	0	0	NA
E. coli	97.1% (132/136)	99.3% (135/136)	2	0	1
K. oxytoca	100.0% (31/31)	100.0% (31/31)	0	0	NA
K. pneumoniae	96.1% (123/128)	99.2% (127/128)	10	0	1
M.morganii	83.9% (26/31)	100.0% (31/31)	0	0	NA
P. mirabilis	34.3% (12/35)	97.1% (34/35)	0	1	NA
P. rettgeri	81.0% (17/21)	100.0% (21/21)	0	0	NA
P. stuartii	90.5% (19/21)	100.0% (21/21)	0	0	NA
S. marcescens	96.8% (30/31)	100.0% (31/31)	0	0	NA

Table 2: Performance per Enterobacterales species

Organisms	ETEST MIC	BMD MIC	Genotypes
E. coli	8	16	NDM-7, CMY-42
E. coli	>=64	>64	NDM-5, TEM-1B, CMY-42
K. pneumoniae	8	64	NDM-1, OXA-9, TEM-1A, CTX-M15, SHV-11, OXA-1
K. pneumoniae	>=64	>64	NDM-1, CMY-4, CTX-M-15, SHV-11, OXA-10
K. pneumoniae	8	16	OXA-181, CTX-M-15, SHV-26
K. pneumoniae	>=64	>64	NDM-1, OXA-232, OXA-9, TEM-1A, CTX-M-15, SHV-11, OXA-1
K. pneumoniae	>=64	>64	OXA-232, CTX-M-15, SHV-1, OXA-1
K. pneumoniae	>=64	>64	VIM-1, SHV
K. pneumoniae	>=64	>64	VIM-1, SHV-11
K. pneumoniae	>=64	>64	TEM, SHV, CTX-M-15, OXA-48
K. pneumoniae	>=64	>64	TEM, SHV, NDM-1 CTX-M-15, OXA-232
K. pneumoniae	16	32	NDM-1 TEM SHV CTX-M-15 CMY

Table 3: Resistant strains Characterizations

ETEST® MEV performance for *P. aeruginosa* met ISO acceptance criteria for EA (≥90%), CA (≥90%), ME (≤3%) and VME (≤3%). For Enterobacterales*, ETEST® MEV performances met ISO criteria for EA, CA and ME, but not for VME, with a rate of 16.7% (2/12). For the 2 VME observed, ETEST® MEV MIC were both 8 mg/L and BMD MIC were 16 and 64 (Tables 3 & 4). As there is no intermediate category in EUCAST breakpoints, both were considered as VME. Despite a trend in underestimating MIC observed for 41% of the Enterobacterales, ETEST ® MEV met the ISO criteria for EA. This underestimation remained one doubling dilution apart from the BMD in 91%, i.e., within EA. So, using an alternative testing/reference method prior to reporting results for Enterobacterales when the ETEST® MEV MIC is 8 mg/L is recommended.

* As overall EA for *P. mirabilis* species was only 34.3%, this species was removed from the intended use of the device label.

BMD, Reference MIC

ETEST MIC	<=0.004 S	0.008 S	0.016 S	0.032 S	0.064 S	0.125 S	0.25 S	0.5 S	1 S	2 S	4 S	8 S	16 R	32 R	>=64 R
< 0.004 S															
0.004 S															
0.008 S		1	6		1										
0.016 S	1		111	136	2	1	1								
0.032 S			6	157	37	6						1			
0.064 S				3	22	26	5								
0.125 S				1		9	6								
0.25 S						3	3	5		1					
0.5 S						1		7	2						
1 S								1	5		2				
2 S								1	2	5	3				
4 S											1				
8 S												1	1		1
16 R														1	
32 R															
≥64 R															
Evaluable results	1	123	297	62	46	15	14	9	6	6	2	1	1		

Table 4: Frequency table for Enterobacterales (excluding *P. mirabilis*)

BMD, Reference MIC

ETEST MIC	<=0.004 S	0.008 S	0.016 S	0.032 S	0.064 S	0.125 S	0.25 S	0.5 S	1 S	2 S	4 S	8 S	16 R	32 R	>=64 R
< 0.004 S															
0.004 S															
0.008 S															
0.016 S			2												
0.032 S				1	3										
0.064 S				1	4	5	1								
0.125 S					5	15	7	1							
0.25 S						7	18	6	2						
0.5 S							13	14	2						
1 S								9	5	2					
2 S									3	6	3				
4 S											4				
8 S											3	1			
16 R											2	2			
32 R													3		
≥64 R													5	4	4
Evaluable results	2	2	12	27	39	30	12	8	12	3	8				

Table 5: Frequency table for *P. aeruginosa*

CONCLUSION

When compared to the reference method, results of this multicentre trial support the accuracy of ETEST® MEV for determining the MIC of Enterobacterales and *P. aeruginosa* in a clinical setting. The new ETEST® MEV can be considered as substantially equivalent to BMD.

ACKNOWLEDGEMENTS

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