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Multilab evaluation of delafloxacin MIC Test Strip against Gram-negative and Gram-positive organisms

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ABSTRACT

The performance of the delafloxacin MIC Test Strip (MTS) was evaluated. Three testing sites collected/tested clinical isolates, and 1 site tested challenge isolates that together total 224 *S. aureus*, 36 *S. haemolyticus*, 23 *S. lugdunensis*, 105 *E. faecalis*, 308 Enterobacteriales, and 140 *P. aeruginosa*. MIC testing was performed by broth microdilution (BMD) and MTS. Each site also tested 20 common isolates in triplicate on 3 days by MTS and 20 replicates of 4 QC strains by MTS and BMD. MTS results for consolidated clinical/challenge isolates were within 1 doubling dilution of the BMD MIC for 96.9% of *S. aureus*; 100% of *S. haemolyticus*, *S. lugdunensis*, and *E. faecalis*; 98.4% of Enterobacteriales; and 97.9% of *P. aeruginosa*. All reproducibility results were within 1 dilution of the modal MIC. All BMD and MTS results for the QC strains were within expected ranges. Overall, the delafloxacin MTS performed similar to BMD.

1. Introduction

Delafloxacin is a fluoroquinolone antimicrobial agent with broad-spectrum antimicrobial activity, including activity against methicillin-resistant *Staphylococcus aureus* (MRSA), a favorable tolerability profile, and administration of both intravenous and oral forms. One unique difference to the other fluoroquinolones is that delafloxacin is anionic, which, in vitro, allows for increased accumulation in bacteria (Mogle et al. 2018). Delafloxacin was approved by U.S. FDA in June 2017 for the treatment of acute bacterial skin and skin structure infection. A Phase 3 trial for community-acquired bacterial pneumonia has been completed.

Liofilchem (Waltham, MA) provides MIC test strips for in vitro susceptibility testing for a variety of antimicrobial agents. The Liofilchem MIC Test Strip (MTS) is a quantitative agar-based diffusion assay for determining the minimum inhibitory concentration (MIC). The strips are made of a special high-quality paper impregnated with a predefined concentration gradient of antibiotic across 15 two-fold dilutions like those of a conventional MIC method. This multilab study was performed to compare the delafloxacin MTS to CLSI reference broth microdilution (BMD).

2. Methods

Gram-positive and Gram-negative clinical isolates were collected and tested in 2 separate studies. Two sites were involved in both the Gram-positive and Gram-negative studies: Laboratories Specialists, Inc. (LSI), Westlake, OH (with recent isolates collected from University Hospitals, Cleveland, OH), and University of Rochester, Rochester, NY. A third site was Cincinnati Children's Hospital & Medical Center, Cincinnati, OH, for the Gram-positive study and Wake Forest University Health Sciences Medical Center (Winston-Salem, NC) for the Gram-negative study. The reference MIC method was performed with frozen plates according to the CLSI BMD guidelines, and the MTS was tested according to manufacturer's instructions (CLSI 2015; CLSI 2017). Frozen BMD plates (ThermoFisher, Oakwood Village, OH) were prepared using Difco brand cation adjusted Mueller Hinton broth (CAMHB; BD, Sparks, MD). Each of the 3 testing sites utilized BBL brand MHA (BD, Sparks, MD). The testing and analysis protocols were based on the FDA AST guidance document (Center for Devices and Radiological Health, Food and Drug Administration 2009). Categorical agreements and error rates were based on the delafloxacin FDA breakpoints [staphylococci and Enterobacteriaceae (*E. coli, K. pneumoniae*, and *E. cloacae*): ≤0.25 susceptible, 0.5 intermediate, ≥1 resistant; enterococci: ≤0.25 susceptible, 0.5 intermediate, ≥1 resistant; *P. aeruginosa* ≤0.5 susceptible, 1 intermediate, ≥2 resistant]. Each of the 3 collecting/testing sites was

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requested to collect a minimum of 100 Gram-positive isolates (to include methicillin-susceptible and methicillin-resistant *S. aureus, Enterococcus faecalis, Staphylococcus haemolyticus, Staphylococcus hominis*, and *Staphylococcus lugdunensis)* and 100 Gram-negative isolates [to include *Enterobacter cloacae*, *Escherichia coli, Klebsiella* (*Enterobacter*) *aerogenes, Klebsiella pneumoniae, Klebsiella oxytoca, Proteus mirabilis*, and *Pseudomonas aeruginosa*] and test them by both delafloxacin BMD and MTS methods. In addition, for verification of reproducibility, Gram-positive and Gram-negative sets of 10 isolates each were sent to each of the 3 sites, and each site tested them in triplicate on 3 days by delafloxacin MTS. LSI also tested challenge isolates by delafloxacin BMD and MTS (species as listed in Table 2), which included a majority of delafloxacin-resistant isolates (among 126 Gram-positive challenge isolates, 100 were resistant and included 45 *S. aureus*, 15 *S. haemolyticus*, 3 *E. faecalis*, and 37 vancomycin-resistant *E. faecium*, and among 88 Gram-negative challenge isolates, 76 were resistant and included 59 Enterobacteriales and 17 *P. aeruginosa*). The overall essential agreement (EA) was calculated based on all results, which included the evaluation of the off-scale results as follows: BMD results of ≤0.002 and 0.004 μg/mL were within EA of MTS results at ≤0.002 and 0.004 μg/mL; BMD results of 16 and ≥ 32 μg/mL were within EA of MTS results at 16 and ≥32 μg/mL. EA based on evaluable results excluded BMD MIC result of ≤0.002 and ≥32 μg/mL, as well as BMD MIC results of 0.004 μg/mL/MTS of ≤0.002 μg/mL and BMD of 16 μg/mL/MTS of ≥32 μg/mL.

A slight trend of lower delafloxacin BMD MIC results for staphylococci with the use of Difco brand CAMHB (BD, Sparks, MD) was recently reported by other investigators (data not shown). As a result of this observation, LSI tested 30 method verification isolates with frozen MIC panels made by LSI with Difco CAMHB and compared results with the modal MIC values for each of the 30 isolates. The modal MIC values were based on a minimum of 10 replicates tested at LSI using frozen MIC panels with BD brand CAMHB (BD, Sparks, MD).

3. Results

3.1. Gram-positive organisms

All delafloxacin BMD and MTS results were within the expected ranges for quality control strains *Staphylococcus aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212 (Table 1). For both QC strains, the majority of MTS results were in the middle of the expected ranges [85.3% of *S. aureus* MIC results were 0.004 μg/mL, and 81.8% of *E. faecalis* results were 0.06 μg/mL (high end of midrange)]. The isolates were tested within 7 days of collection for 35.1%, within 1 year for 40.8%, and within 3 years for 24.1% of all clinical isolates. The majority of BMD results for *S. aureus* were at the low end of the expected range (78.7% were ≤0.002 μg/mL), and the majority of BMD results for *E. faecalis* were in the middle of the expected range [74.2% were 0.03 μg/mL (low end of midrange)]. Inter- and intralaboratory precision was excellent for the 10 Gram-positive reproducibility strains; all results were within ±1 dilution of the modal MIC. Essential agreement rates for consolidated clinical and challenge isolates were 100% for all Gram-positive species, with exception of *S. aureus* which was 97.4% (Table 3, Fig. 1). Although the EA was 100% for the combined set of 36 clinical and challenge *S. haemolyticus*, the category error rate of 66.7% was attributed to a relatively large percentage of strains (72%) with BMD results at or near the breakpoint of which 12/26 were considered minor errors. A trend toward slightly higher *S. aureus* and slightly lower *S. lugdunensis* MTS MIC results compared to BMD MIC results was noted (Table 3). Among 209 clinical and challenge *S. aureus*, 44.5% were ≥1 dilution higher compared to 12.0% that were ≤1 dilution lower when compared to the BMD results. Among 23 clinical *S. lugdunensis*, 4.3% were ≥1 dilution higher compared to 60.9% that were ≤1 dilution lower when compared to the BMD results. The mean colony counts (CFU/mL) for the MTS and BMD clinical and challenge isolate testing were 9.4×10^7 and 4.7×10^5 (*S. aureus*, $n = 43$), 7.3×10^7 and 3.6×10^5 (coagulase-negative staphylococci, $n = 8$), and 8.1×10^7 and 4.0×10^5 (*E. faecalis*, $n = 21$).

The subsequent study of Difco CAMHB BMD to BD CAMHB BMD MIC results for 30 method verification isolates showed a trend of lower MIC results with Difco CAMHB. Compared to the modal CAMHB result, the Difco MIC was lower by 1 dilution for 6/10 and similar for 4/10 *E. faecalis*; lower by 1 dilution for 11/16 and similar for 5/16 *S. aureus*; and lower by 2 dilutions for 1/4, lower by 1 dilution for 1/4, and similar for 2/4 *S. haemolyticus*.

3.2. Gram-negative organisms

All delafloxacin BMD and MTS results were within the expected ranges for quality control strains *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 (Table 1). For both QC strains, the majority of MTS and BMD results were in the middle of the expected ranges (77.0%/68.9% of *E. coli* BMD/MTS MIC results were 0.016 μg/mL, and

Table 1
Delafloxacin BMD and MTS MIC results (*n*) for quality control strains.

QC organism	Expected result	MIC	Reference BMD frequency				MTS frequency			
		μg/mL	Site 1	Site 2	Site 3	All Sites	Site 1	Site 2	Site 3	All Sites
S. aureus ATCC 29213	0.001–0.008 μg/mL	**≤0.002**	**9**	**20**	**19**	**48**	**1**	**1**		**2**
		0.004	**10**		**1**	**11**	**22**	**19**	**17**	**58**
		0.008	**2**			**2**	**5**		**3**	**8**
		0.016								
E. faecalis ATCC 29212	0.016–0.12 μg/mL	0.008								
		0.016								
		0.03	**6**	**20**	**20**	**46**	**6**	**4**	**2**	**12**
		0.06	**16**			**16**	**20**	**16**	**18**	**54**
		0.12								
		0.25								
E. coli ATCC 25922	0.008–0.03 μg/mL	0.004								
		0.008					**4**			**4**
		0.016	**11**	**18**	**18**	**47**	**13**	**10**	**19**	**42**
		0.03	**10**	**2**	**2**	**14**	**4**	**10**	**1**	**15**
		0.06								
P. aeruginosa ATCC 27853	0.12–0.5 μg/mL	0.06								
		0.12	**2**			**2**	**9**		**2**	**11**
		0.25	**13**	**20**	**20**	**53**	**12**	**20**	**18**	**50**
		0.5	**6**			**6**				
		1								

Bolded lines and values represent the expected CLSI ranges (CLSI 2015).

(a) *S. aureus* (MSSA and MRSA; *n* = 224)

MTS Results	BMD Reference Results														
	≤0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	≥32
≤0.002	14	2													
0.004	34	23	4	1											
0.008	5	13	1												
0.016				1											
0.03															
0.06					3	2	1								
0.12						13	16	3							
0.25						1	8	10	4						
0.5								9	7	1					
1										2	1				
2											12	8			
4											4	16			
8												2	1		
16														1	1
≥32															

(b) *S. aureus* (MRSA; *n* = 142)

MTS Results	BMD Reference Results														
	≤0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	≥32
≤0.002	3														
0.004	13	8	1												
0.008	2	7	1												
0.016				1											
0.03															
0.06					2	2	1								
0.12						12	15	2							
0.25							7	6	2						
0.5								8	6						
1										1	1				
2											12	8			
4											4	14			
8												1	1		
16															
≥32															1

(c) *S. haemolyticus* (*n* = 36)

MTS Results	BMD Reference Results														
	≤0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	≥32
≤0.002	1														
0.004	4	1	1												
0.008		1													
0.016															
0.03															
0.06															
0.12															
0.25								2	3						
0.5								1	6	8					
1											2				
2											1				
4												2	1		
8												1			
16													1		
≥32															

(d) *S. lugdunensis* (*n* = 23)

MTS Results	BMD Reference Results														
	≤0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	≥32
≤0.002															
0.004		1	2												
0.008			4	8											
0.016			1	2	2										
0.03															
0.06							1								
0.12															
0.25															
0.5									1	1					
1															
2															
4															
8															
16															
≥32															

(e) *E. faecalis* (*n* = 105)

MTS Results	BMD Reference Results														
	≤0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	≥32
≤0.002															
0.004			1												
0.008															
0.016					1										
0.03					11	6									
0.06					6	38	9								
0.12						7	6								
0.25							1		2						
0.5								2	5						
1									3	3	2				
2										1					
4															
8														1	
16															
≥32															

(f) *E. faecalis* and *E. faecium* (*n* = 142)

MTS Results	BMD Reference Results														
	≤0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	≥32
≤0.002															
0.004			1												
0.008															
0.016					1										
0.03					11	6									
0.06					6	38	9								
0.12						7	6								
0.25							1		2						
0.5								2	5						
1									3	3	2				
2										1					
4															
8														4	
16														1	
≥32															33

Fig. 1. Comparison of delafloxacin MTS MIC distribution to BMD MIC distribution (*n*) for staphylococci and enterococci (consolidated clinical and challenge isolates).

86.9/82.0% of *P. aeruginosa* results were 0.25 μg/mL). Inter- and intralaboratory precision was excellent for the 10 Gram-positive reproducibility strains; all results were within ±1 dilution of the modal MIC. The Enterobacteriales and *P. aeruginosa* isolates were tested within 6 months of collection for 70.8% and 55.0% of all clinical isolates, respectively. EA rates for consolidated clinical and challenge Enterobacteriales and *P. aeruginosa* were 98.4% and 97.9%, respectively (Table 2, Fig. 2). Among the individual species of Enterobacteriales, EA rates for the consolidated clinical and challenge isolates ranged from 96.3% (*K. pneumoniae*) to 100% (*E. cloacae, K. aerogenes K. oxytoca*, and *P. mirabilis*). There was no significant trending of MTS compared to BMD results noted for Enterobacteriales and *P. aeruginosa* (difference between % of ≤1 and ≥1 dilution was <±30%) (Table 3). The mean colony counts (CFU/mL) for the MTS (inoculum tube) and BMD (positive grown control well) for clinical and challenge isolate testing were 6.7×10^7 and 3.4×10^5 (Enterobacteriales, $n = 34$), and 9.0×10^7 and 4.5×10^5 (*P. aeruginosa*, $n = 14$).

4. Discussion

The current wave of antimicrobial development is a promising and timely change of events in the war against bacterial antimicrobial resistance. The detection of resistance with existing and new antimicrobial agents is instrumental for both optimal patient care and success in identifying and controlling the spread of resistance. Gradient strip testing provides a relatively simple, manual MIC method that can be used as a supplemental method to automated methods. As the delay in introduction of new agents into automated antimicrobial susceptibility systems continues to exist, this methodology can provide a welcome means of testing agents soon after they are cleared for use (Humphries and Hindler 2016). Evaluation of antimicrobial susceptibility testing should include testing and analysis of the most important variables that can impact the MIC, which continues to be an area of current discussion among regulators and investigators and was recently undertaken by a CLSI working group (Humphries et al. 2018). The FDA guidance document for evaluating antimicrobial susceptibility testing provides an effective methodology of comparison of commercial methods to reference methods, and since the current version of the guidance document, the FDA Center for Devices and Radiological Health continues to modify their requirements and review process to better assure optimal performance and understanding of any limitations (Center for Devices and Radiological Health, Food and Drug Administration 2009).

With regard to this delafloxacin MTS study, a limitation was noted by FDA that resistant strains were not molecularly characterized according to the common fluoroquinolone-resistant mechanisms (i.e., DNA gyrase, topoisomerase IV, and genes that affect the expression of diffusion channels in the outer membrane and multidrug-resistance efflux systems). Two resistant *K. aerogenes* were tested as part of the challenge isolate set and were effectively detected by delafloxacin MTS; however, because the number of resistant strains was limited, a notation in the label relative to the lack of resistant isolates for this species was included. The broth used for the BMD method in the delafloxacin 510(k) was Difco brand, and as was shown in a separate follow-up study with the set of 30 Gram-positive method verification isolates, there was a bias toward slightly lower MIC results with Difco compared to MIC results with BD CAMHB. The use of Difco CAMHB may be a factor in the trending of slightly higher MTS compared to BMD for staphylococci observed in the 510(k) study.

Overall, the delafloxacin MTS performed well in comparison to reference BMD for all species tested. This FDA-cleared method was shown to be a reliable method for testing delafloxacin MIC against relevant clinical isolates.

Table 2
Summary table of delafloxacin MTS MIC compared to BMD MIC by bacterial species.

Bacterial species	Total tested	#EA	%EA	Total EVAL	#EA EVAL	%EA EVAL	#CA	%CA	#R	#VME	#ME	#mE
Clinical data												
S. aureus	169	161	95.3	114	111	97.4	158	93.5	4	0	0	11
S. aureus, MSSA	75	69	92	38	35	92.1	73	97.3	2	0	0	2
S. aureus, MRSA	94	92	97.9	76	76	100	85	90.4	2	0	0	9
S. haemolyticus	15	15	100	10	10	100	13	86.7	1	0	0	2
S. lugdunensis	15	15	100	15	15	100	NA	NA	NA	NA	NA	NA
E. faecalis	100	100	100	100	100	100	95	95	14	0	0	5
Enterobacteriales	240	237	98.8	230	227	98.7	236	98.3	60	0	0	4
E. cloacae	45	45	100	42	42	100	44	97.8	7	0	0	1
E. coli	90	89	98.9	88	87	98.9	89	98.9	32	0	0	1
K. aerogenes	15	15	100	15	15	100	13	86.7	0	0	0	2
K. oxytoca	15	15	100	14	14	100	15	100	5	0	0	0
K. pneumoniae	60	58	96.7	56	54	96.4	60	100	11	0	0	0
Proteus mirabilis	15	15	100	15	15	100	15	100	5	0	0	0
P. aeruginosa	120	119	99.2	113	112	99.1	112	93.3	31	0	0	8
Total	**659**	**647**	**98.2%**	**582**	**575**	**98.8%**	**614**	**93.2%**	**110**	**0**	**0**	**30**
Challenge data												
S. aureus	55	55	100	54	54	100	52	94.5	45	0	0	3
S. aureus, MSSA	7	7	100	7	7	100	5	71.4	4	0	0	2
S. aureus, MRSA	48	48	100	47	47	100	47	97.9	41	0	0	1
S. haemolyticus	21	21	100	21	21	100	11	52.4	15	0	0	10
S. lugdunensis	8	8	100	8	8	100	NA	NA	NA	NA	NA	NA
Enterococcus species	42	42	100	9	9	100	42	100	40	0	0	0
E. faecalis	5	5	100	5	5	100	5	100	3	0	0	0
E. faecium	37	37	100	4	4	100	37	100	37	0	0	0
Enterobacteriales	68	66	97.1	53	51	96.2	66	97.1	59	0	0	2
E. cloacae	14	14	100	10	10	100	14	100	13	0	0	0
E. coli	21	20	95.2	18	17	94.4	21	100	21	0	0	0
K. aerogenes	5	5	100	3	3	100	5	100	2	0	0	0
K. oxytoca	5	5	100	5	5	100	4	80.0	1	0	0	1
K. pneumoniae	20	19	95.0	14	13	92.9	19	95.0	19	0	0	1
P. mirabilis	3	3	100	3	3	100	3	100	3	0	0	0
P. aeruginosa	20	18	90.0	7	5	71.4	20	100	17	0	0	0
Total	**214**	**210**	**98.1%**	**152**	**148**	**97.4%**	**191**	**89.3%**	**176**	**0**	**0**	**15**

EA = essential agreement, EVAL = evaluable results, CA = category agreement, R = resistant, VME = very major errors, ME = major errors, mE = minor errors, NA = not applicable (no breakpoints).

(a) *E. coli* (*n* = 111)

MTS Results	BMD Reference Results														
	≤0.002	0.004	0.008	0.02	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	≥32
≤0.002															
0.004															
0.008															
0.016				5											
0.03				6	20	3									
0.06					3	4	1								
0.12						1	4	1							
0.25							1	7	1						
0.5									1						
1										2	2				
2										1	1	2			
4										1	5	8	3		
8												5	6	1	
16													8	2	
≥32													1	1	4

(b) *K. pneumoniae* (*n* = 80)

MTS Results	BMD Reference Results														
	≤0.002	0.004	0.008	0.02	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	≥32
≤0.002															
0.004															
0.008															
0.016															
0.03				1	1										
0.06				2	1	20	2								
0.12							18								
0.25								2							
0.5									3	1					
1															
2											3	2			
4											1	3	1		
8												1	3	2	
16													1	1	
≥32													1	2	8

(c) Enterobacteriales (*n* = 308)

MTS Results	BMD Reference Results														
	≤0.002	0.004	0.008	0.02	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	≥32
≤0.002															
0.004															
0.008															
0.016				6											
0.03				7	27	5									
0.06				2	7	45	11								
0.12						6	41	4							
0.25							1	16	5						
0.5									6	1					
1										5	3				
2										2	9	7			
4										1	8	16	5		
8												8	10	4	
16													9	4	1
≥32													2	4	20

(d) *P. aeruginosa* (*n* = 140)

MTS Results	BMD Reference Results														
	≤0.002	0.004	0.008	0.02	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	≥32
≤0.002															
0.004															
0.008															
0.016															
0.03					1										
0.06						1	2								
0.12							19	5							
0.25							1	28	7						
0.5								1	12	3					
1									1	9	2				
2										2	3	2			
4											4	6	3		
8											1	2	1		
16													2		
≥32													2	10	10

Bold lines in each scatterplot indicate delafloxacin FDA MIC breakpoints

Fig. 2. Comparison of delafloxacin MTS MIC distribution to BMD MIC distribution (*n*) for Enterobacteriales and *P. aeruginosa* (consolidated clinical and challenge isolates).

Table 3
Trending analysis of delafloxacin MTS MIC compared to BMD MIC by bacterial species for combined challenge and clinical isolates.

Organism species	Difference between MTS compared to BMD (*n*)					Total (*n*)	Difference between % of ≤1 and ≥1
	≤2 Dilutions lower	1 Dilution lower	Similar	1 Dilution higher	≥2 Dilutions higher		
Gram-positive:							
S. aureus	1	24	91	87	6	209	32.5%
S. aureus (MSSA)	1	9	24	32	5	71	38.0%
S. aureus (MRSA)	0	15	67	54	2	138	29.7%
S. haemolyticus	0	15	12	8	0	35	−20.0%
S. lugdunensis	0	14	8	1	0	23	−56.5%
E. faecalis	0	22	63	20	0	105	−1.9%
Gram-negative:							
Enterobacteriales	0	46	185	52	5	288	3.8%
E. cloacae	0	14	32	6	0	52	−15.4%
E. coli	0	14	60	31	2	107	17.8%
K. aerogenes	0	4	14	2	0	20	−10.0%
K. oxytoca	0	3	13	3	0	19	0.0%
K. pneumoniae	0	8	54	7	3	72	2.8%
P. mirabilis	0	3	12	3	0	18	0.0%
P. aeruginosa	0	24	80	23	3	130	1.5%

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