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Activity of Delafloxacin When Tested against Bacterial Surveillance Isolates Collected in the US and Europe during 2014–2016 as Part of a Global Surveillance Program

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Abstract

Background: Delafloxacin (DLX) is a novel anionic fluoroquinolone that was recently approved (June 2017) by the US FDA to treat acute bacterial skin and skin structure infections and is undergoing Phase 3 studies to treat community-acquired bacterial pneumonia.

Methods: A total of 36,683 Gram-positive (GP) and -negative (GN) bacteria isolated during 2014-2016 were selected from medical centers in the US and Europe. Susceptibility testing (S) was performed by frozen-form broth microdilution methods for DLX and comparators.

Results: DLX was very active against *Staphylococcus aureus* (SA, n= 9,355; $MIC_{50/90}$, 0.008/0.5 µg/mL) whereas the levofloxacin (LEV) $MIC_{50/90}$ was 0.25/>4 µg/mL (67.9%S). The $MIC_{50/90}$ for methicillin-resistant SA (MRSA) was 0.12/1 µg/mL. For MRSA, all isolates were S to vancomycin and daptomycin (DAP), linezolid and tigecycline (TGC) S was ≥99.9%. Decreased rates of S were noted for LEV (29.8%), clindamycin (72.9%), and erythromycin (17.3%/17.8%; CLSI/EUCAST). Minocycline ($MIC_{50/90}$, 0.12/0.25 µg/mL), ceftaroline ($MIC_{50/90}$, 0.25/0.5 µg/mL), DAP ($MIC_{50/90}$, 0.5/0.5 µg/mL), and DLX ($MIC_{50/90}$, 0.015/0.5 µg/mL) were the most active agents tested against coagulase-negative staphylococci. Against *Streptococcus pneumoniae* (SPN), the $MIC_{50/90}$ for DLX (0.015/0.03 µg/mL) and TGC (0.03/0.06 µg/mL) were the lowest among the agents tested. The DLX $MIC_{50/90}$ values did not vary among the penicillin-S, -intermediate, and -R subgroups of SPN. The $MIC_{50/90}$ values for DLX against *S. pyogenes* and *S. agalactiae* were 0.015/0.03 µg/mL. DLX was highly active against *Haemophilus influenzae*. The DLX $MIC_{50/90}$ (≤0.001/0.004 µg/mL) was the same for β-lactamase positive and negative *H. influenzae*. Against *Enterobacteriaceae*, 76.0% of DLX MIC values were ≤1 µg/mL. Susceptibility to LEV was 80.8%, and S to ceftriaxone, ceftazidime (CAZ), and cefepime ranged from 78.5%-86.3%. A total of 72.6% of *Pseudomonas aeruginosa* isolates exhibited DLX MIC values ≤1 µg/mL, while LEV S was 73.2% and CAZ was 81.6%. The MIC_{50} for both DLX and LEV were 0.5/>4 µg/mL, respectively.

Conclusions: DLX was active against a broad range of GP and GN bacteria, including MRSA and multidrug-resistant SPN. DLX merits further study as therapy in infections in which these organisms may occur.

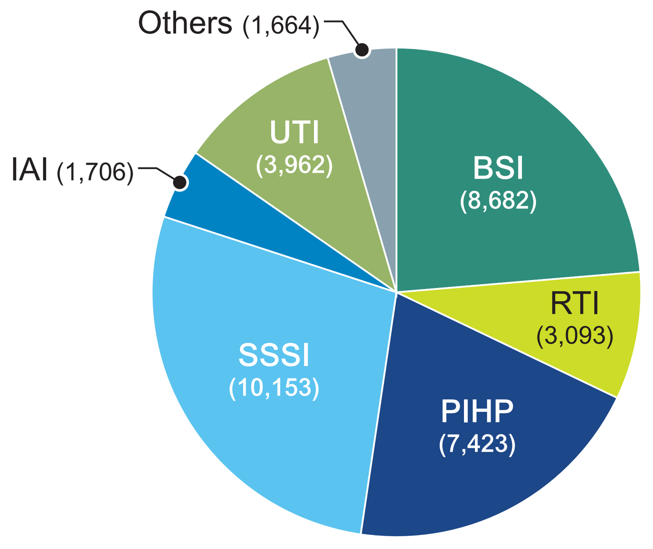
Introduction

- Delafloxacin is a broad-spectrum fluoroquinolone (FQ) antibacterial that was recently approved (June 2017) by the US Food and Drug Administration to treat acute bacterial skin and skin structure infections (ABSSSI) and is undergoing clinical development for use in the treatment of hospitalized community-acquired pneumonia
- Delafloxacin has potent activity against ABSSSI pathogens, including methicillin-resistant (MRSA) and fluoroquinolone-resistant (FQ-R) *Staphylococcus aureus*
- Delafloxacin is also active against bacteria associated with hospital- and community-acquired respiratory tract infections, including activity against FQ-R *Streptococcus pneumoniae* and *Haemophilus influenzae*
- In this study, *in vitro* susceptibility was determined for delafloxacin and comparator agents against clinical isolates collected from patients in the US and Europe as part of the SENTRY surveillance program during 2014–2016

Materials and Methods

- A total of 14,906 bacterial isolates from Europe and 21,777 from the US were collected from patients during 2014–2016 as part of the SENTRY Antimicrobial Surveillance Program
  - The number of organisms from each infection type is shown in Figure 1

Figure 1 Number of isolates per infection type



PIHP—pneumonia in hospitalized patients
SSSI—skin and skin structure infections
RTI—respiratory tract infections caused by *S. pneumoniae*, *Haemophilus* spp., or *Moraxella catarrhalis*
BSI—bloodstream infections
UTI—urinary tract infections
IAI—intra-abdominal infections

- Isolates were designated by the site as pathogens and were non-duplicate (1 per infection episode)
- Species identification was performed at the participant medical centers and confirmed at the monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) using standard biochemical tests or matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker, Billerica, Massachusetts, USA), following the manufacturer's instructions
- Clinical isolates and quality control organisms were tested for susceptibility to delafloxacin and comparators according to CLSI guidelines using broth microdilution panels
  - CLSI (2017) and EUCAST (2017) interpretive criteria were applied
  - Quality control organisms were tested concurrently with clinical isolates

Results

- Quality control for delafloxacin was in-range for 98.1% of tests
  - The overall trend for QC was at the higher end of the range
  - For *S. aureus* ATCC 29213, the modal MIC value was 0.004 µg/mL (range 0.001-0.008 µg/mL)
- Delafloxacin was very active against *S. aureus* (MIC_{50}/MIC_{90}, 0.008/0.5 µg/mL) and CoNS (MIC_{50}/MIC_{90}, 0.015/0.5 µg/mL; Tables 1 and 2)
  - A total of 88.9% *S. aureus* isolates were inhibited by delafloxacin at ≤0.25 µg/mL (6.4% of isolates were resistant; Table 1)
- Delafloxacin was the most potent antimicrobial when tested against methicillin-susceptible *S. aureus* (MSSA; $MIC_{50/90}$ ≤0.004/0.015 µg/mL)
  - Based on MIC_{90}, delafloxacin was 16-fold more potent against MSSA than ceftaroline and 32-fold more potent than levofloxacin (Table 1; data not shown)
- Against MRSA isolates, tigecycline ($MIC_{50/90}$, 0.06/0.12 µg/mL), delafloxacin ($MIC_{50/90}$, 0.12/1 µg/mL), trimethoprim-sulfamethoxazole ($MIC_{50/90}$, ≤0.5/≤0.5 µg/mL), minocycline (≤0.06/0.25 µg/mL), and daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/mL) were the most potent antimicrobials (Table 2)
  - Delafloxacin was 32-fold more potent than levofloxacin (by MIC_{50}) and greater than 4-fold more potent by MIC_{90} criteria (Table 2)
- MRSA exhibited high levels of resistance against levofloxacin (CLSI/EUCAST, 68.4%/70.2% resistant) and erythromycin (77.7%/80.6% [CLSI/EUCAST]; Table 2)
- The greatest coverage of all *S. aureus* (MSSA and MRSA) was provided by vancomycin (100.0% susceptible) and daptomycin, linezolid, and tigecycline, which all exhibited >99.9% susceptibility (Table 2)
  - Trimethoprim-sulfamethoxazole ($MIC_{50/90}$, ≤0.5/≤0.5 µg/mL) provided 98.7% coverage and ceftaroline ($MIC_{50/90}$, 0.25/1 µg/mL) 98.1% coverage (Table 2)
- The majority of *Enterococcus faecalis* isolates exhibited relatively low delafloxacin MIC results ($MIC_{50/90}$, 0.12/1 µg/mL) contrasting with *Enterococcus faecium* MIC values ($MIC_{50/90}$ >4/>4 µg/mL) (Table 1)
  - 45.5%/45.9% (CLSI/EUCAST) *E. faecium* were vancomycin-resistant (data not shown)
- Delafloxacin was the most active agent tested against *S. pneumoniae* ($MIC_{50/90}$, 0.015/0.03 µg/mL; Tables 1 and 2)
  - Only 2 isolates exhibited a delafloxacin MIC of >0.25 µg/mL (Table 1)
  - Delafloxacin was 4-fold more active than ceftaroline (MIC_{90}, 0.12 µg/mL; 99.9% susceptible), 8-fold more active than moxifloxacin (MIC_{90}, 0.25 µg/mL; 99.1% susceptible), and 32-fold more active than levofloxacin (MIC_{90}, 1 µg/mL; 98.7% susceptible; Table 2)
  - 5 isolates had penicillin MIC values of 8 µg/mL (high-level penicillin resistance; resistant to parenteral penicillin), the delafloxacin MIC results ranged from 0.008–0.03 µg/mL, and the ceftriaxone MIC values ranged from 2-8 µg/mL
- Delafloxacin ($MIC_{50/90}$, 0.015/0.06 µg/mL) and tigecycline ($MIC_{50/90}$, 0.03/0.06 µg/mL) were the most active agents tested against viridans group streptococci (data not shown) and were very potent against *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Streptococcus dysgalactiae* (Tables 1 and 2)
  - 98.7% of *S. agalactiae* isolates were susceptible to delafloxacin (Table 2)
- Delafloxacin was active against the majority of *Enterobacteriaceae*, exhibiting $MIC_{50/90}$ values of 0.12/4 µg/mL; 66.7% of isolates were susceptible (Table 3)
  - Ciprofloxacin and levofloxacin susceptibilities against *Enterobacteriaceae* were 78.6%/74.4% and 80.8%/76.3%, respectively (CLSI/EUCAST) (Table 3)
  - Fluoroquinolone activity decreased against ESBL-producing *Enterobacteriaceae* (data not shown)
  - Delafloxacin was more active against non-ESBL *Escherichia coli* ($MIC_{50/90}$, 0.06/4 µg/mL; 77.3% susceptible) and non-ESBL *Klebsiella pneumoniae* ($MIC_{50/90}$, 0.12/0.5 µg/mL; 88.5% susceptible) (Table 1)
- Against *Pseudomonas aeruginosa*, ciprofloxacin ($MIC_{50/90}$, 0.12/>4 µg/mL) based on MIC_{50} value was 4-fold more active than delafloxacin ($MIC_{50/90}$, 0.5/>4 µg/mL) and levofloxacin ($MIC_{50/90}$, 0.5/>4 µg/mL)
  - Susceptibility of *P. aeruginosa* to delafloxacin was 63.6%; ciprofloxacin and levofloxacin susceptibilities were 76.7%/72.3% and 73.2%/65.0% (CLSI/EUCAST), respectively (Table 3)
- *Acinetobacter baumannii* isolates were resistant to many agents
  - Delafloxacin inhibited 30.4% of isolates at ≤0.5 µg/mL (Table 1)
  - Ciprofloxacin and levofloxacin susceptibility ranged from 29.4%–30.4% (Table 3)
  - Only colistin ($MIC_{50/90}$, ≤0.5/4 µg/mL; 88.7% susceptible) and minocycline ($MIC_{50/90}$, 2/16 µg/mL; 65.5% susceptible) exhibited susceptibility ≥65.5% (Table 3)

Table 1 MIC distribution of delafloxacin tested against isolates from the US and Europe (2014-2016)

Each cell: No. of isolates / cumulative %.

Organism / organism group (no. of isolates)	≤0.001	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>	MIC_{50}	MIC_{90}
Staphylococcus aureus (9,355)			4,206 45.0	1,883 65.1	272 68.0	73 68.8	293 71.9	810 80.6	776 88.9	446 93.6	275 96.6	170 98.4	133 99.8	18 100.0		0.008	0.5
MRSA (3,553)			605 17.0	396 28.2	57 29.8	43 31.0	237 37.7	669 56.5	635 74.4	383 85.1	236 91.8	154 96.1	121 99.5	17 100.0		0.12	1
MSSA (5,802)			3,601 62.1	1,487 87.7	215 91.4	30 91.9	56 92.9	141 95.3	141 97.7	63 98.8	39 99.5	16 99.8	12 >99.9	1 100.0		≤0.004	0.015
Coagulase-negative staphylococci (1,575)			396 25.1	334 46.3	163 56.7	36 59.0	43 61.7	122 69.5	183 81.1	145 90.3	99 96.6				54 100.0	0.015	0.5
Staphylococcus hemolyticus (188)			23 12.2	27 26.6	2 27.7	1 28.2	1 28.7	7 32.4	42 54.8	61 87.2	16 95.7				8 100.0	0.25	1
Staphylococcus lugdenensis (198)			9 4.5	50 29.8	114 87.4	22 98.5	0 98.5	1 99.0	0 99.0	1 99.5	1 100.0					0.015	0.03
MR-CoNS coagulase-negative staphylococci (928)			136 14.7	143 30.1	37 34.1	11 35.2	40 39.5	111 51.5	173 70.2	136 84.8	90 94.5				51 100.0	0.12	1
Streptococcus pyogenes (1,699)			145 8.5	677 48.4	638 85.9	221 98.9	17 99.9	1 100.0								0.015	0.03
Streptococcus agalactiae (827)			28 3.4	181 25.3	402 73.9	193 97.2	12 98.7	3 99.0	3 99.4	3 99.8					2 100.0	0.015	0.03
Streptococcus dysgalactiae (449)			48 10.7	185 51.9	173 90.4	40 99.3	1 99.6	2 100.0								0.008	0.015
Streptococcus anginosus (194)			59 30.4	72 67.5	52 94.3	10 99.5	1 100.0									0.008	0.015
Streptococcus pneumoniae (2,242)			60 2.7	488 24.4	1,076 72.4	528 96.0	72 99.2	11 99.7	5 99.9	0 99.9	2 100.0					0.015	0.03
Penicillin-susceptible (≤0.06) *Streptococcus pneumoniae* (1,505)			37 2.5	310 23.1	708 70.1	391 96.1	51 99.5	4 99.7	3 99.9	0 99.9	1 100.0					0.015	0.03
Penicillin-intermediate (>0.06, ≤1) *Streptococcus pneumoniae* (510)			19 3.7	136 30.4	268 82.9	72 97.1	9 98.8	4 99.6	1 99.8	0 99.8	1 100.0					0.015	0.03
Penicillin-resistant (>1) *Streptococcus pneumoniae* (227)			4 1.8	42 20.3	100 64.3	65 93.0	12 98.2	3 99.6	1 100.0							0.015	0.03
Enterococcus faecalis (1,334)			2 0.1	6 0.6	4 0.9	50 4.6	332 29.5	486 66.0	139 76.4	82 82.5	147 93.6	82 99.7	4 100.0			0.12	1
Enterococcus faecium (747)			0 0.0	1 0.1	2 0.4	1 0.5	15 2.5	9 3.7	12 5.4	11 6.8	24 10.0	30 14.1	52 21.0		590 100.0	>4	>4
Haemophilus influenzae (969)	648 66.9	202 87.7	80 96.0	27 98.8	6 99.4	3 99.7	3 100.0									≤0.001	0.004
β-lactamase positive *Haemophilus influenzae* (237)	157 66.2	50 87.3	20 95.8	8 99.2	1 99.6	1 100.0										≤0.001	0.004
β-lactamase negative *Haemophilus influenzae* (732)	491 67.1	152 87.8	60 96.0	19 98.6	5 99.3	2 99.6	3 100.0									≤0.001	0.004
Haemophilus parainfluenzae (61)	8 13.1	9 27.9	13 49.2	21 83.6	4 90.2	1 91.8	0 91.8								5 100.0	0.008	0.015
Moraxella catarrhalis (599)	7 1.2	46 8.8	240 48.9	268 93.7	34 99.3	3 99.8	1 100.0									0.008	0.008
Enterobacteriaceae (12,468)			16 0.1	55 0.6	584 5.3	1,974 21.1	2,949 44.7	1,977 60.6	760 66.7	552 71.1	605 76.0	890 83.1	985 91.0		1121 100.0	0.12	4
Escherichia coli (4,436)			10 0.2	41 1.1	467 11.7	1,251 39.9	723 56.2	197 60.6	186 64.8	85 66.7	89 68.7	374 77.2	610 90.9		403 100.0	0.06	4
non-ESBL-phenotype *Escherichia coli* (3,521)			10 0.3	40 1.4	452 14.3	1,197 48.3	687 67.8	176 72.8	158 77.3	74 79.4	51 80.8	208 86.7	287 94.9		181 100.0	0.06	4
ESBL-phenotype *Escherichia coli* (914)			0 0.0	1 0.1	15 1.8	54 7.7	36 11.6	21 13.9	28 17.0	11 18.2	38 22.3	165 40.4	323 75.7		222 100.0	4	>4
Klebsiella pneumoniae (2,417)			1 <0.1	2 0.1	4 0.3	115 5.0	722 34.9	596 59.6	126 64.8	89 68.5	78 71.7	85 75.2	163 82.0		436 100.0	0.12	>4
non-ESBL-phenotype *Klebsiella pneumoniae* (1,681)			1 0.1	2 0.2	4 0.4	112 7.1	702 48.8	553 81.7	114 88.5	71 92.7	44 95.4	24 96.8	26 98.3		28 100.0	0.12	0.5
ESBL-phenotype *Klebsiella pneumoniae* (736)					0 0.0	3 0.4	20 3.1	43 9.0	12 10.6	18 13.0	34 17.7	61 26.0	137 44.6		408 100.0	>4	>4
Klebsiella oxytoca (601)			1 0.2	0 0.2	0 0.2	24 4.2	201 37.6	249 79.0	60 89.0	18 92.0	6 93.0	14 95.3	10 97.0	8 98.3	10 100.0	0.12	0.5
Pseudomonas aeruginosa (2,181)			3 0.1	2 0.2	11 0.7	17 1.5	46 3.6	158 10.9	622 39.4	529 63.6	195 72.6	153 79.6	93 83.9		352 100.0	0.5	>4

Table 2 Activity of delafloxacin and comparator agents against Gram-positive bacteria

Antimicrobial agent	MIC_{50}	MIC_{90}	CLSI[a] %S	CLSI[a] %R	EUCAST[a] %S	EUCAST[a] %R
Staphylococcus aureus (9,355)						
Delafloxacin	0.008	0.5	88.9	6.4 [b]		
Levofloxacin	0.25	>4	67.9	31.1	67.9	32.1
Ceftaroline	0.25	1	98.1	<0.1	98.1	1.9
Clindamycin	≤0.25	>2	87.3	12.5	87.1	12.7
Daptomycin	0.25	0.5	>99.9		>99.9	<0.1
Erythromycin	0.25	>8	51.6	42.9	52.2	45.5
Linezolid	1	1	>99.9	<0.1	>99.9	<0.1
Minocycline	≤0.06	0.12	98.9	0.5	98.0	1.8
Moxifloxacin	≤0.06	4	69.4	20.1	68.9	31.1
Tigecycline	0.06	0.12	>99.9	[b]	>99.9	<0.1
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	98.7	1.3	98.7	1.2
Vancomycin	0.5	1	100.0	0.0	100.0	0.0
MRSA (3,563)						
Delafloxacin	0.12	1	74.4	14.9 [b]		
Levofloxacin	4	>4	29.8	68.4	29.8	70.2
Ceftaroline	0.5	1	94.9	0.1	94.9	5.1
Clindamycin	≤0.25	>2	72.9	26.8	72.8	27.1
Daptomycin	0.25	0.5	99.9		99.9	0.1
Erythromycin	>8	>8	17.3	77.7	17.8	80.6
Linezolid	1	1	>99.9	<0.1	>99.9	<0.1
Minocycline	≤0.06	0.25	98.1	0.8	96.2	3.4
Moxifloxacin	1	>4	31.0	46.3	30.2	69.8
Tigecycline	0.06	0.12	>99.9	[b]	>99.9	<0.1
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	97.2	2.8	97.2	2.5
Vancomycin	0.5	1	100.0	0.0	100.0	0.0
Coagulase-negative staphylococci (1,575)						
Delafloxacin	0.015	0.5				
Levofloxacin	0.25	>4	58.5	38.1	58.5	41.5
Ceftaroline	0.25	0.5				
Clindamycin	≤0.25	>2	75.8	22.9	74.7	24.2
Daptomycin	0.5	0.5	99.8		99.8	0.2
Erythromycin	>8	>8	40.3	57.3	40.8	58.5
Linezolid	0.5	1	99.3	0.7	99.3	0.7
Minocycline	0.12	0.25	99.6	0.0	99.5	0.4
Moxifloxacin	0.12	4	61.1	29.5	55.1	44.9
Tigecycline	0.06	0.12			100.0	0.0
Trimethoprim-sulfamethoxazole	≤0.5	>4	73.1	26.9	73.1	13.3
Vancomycin	1	2	100.0	0.0	100.0	0.0
Methicillin-resistant CoNS (928)						
Delafloxacin	0.12	1				
Levofloxacin	4	>4	34.6	60.0 [b]	34.6	65.4
Ceftaroline	0.25	1				
Clindamycin	≤0.25	>2	64.0	34.4	62.4	36.0
Daptomycin	0.5	0.5	99.8		99.8	0.2
Erythromycin	>8	>8	19.9	76.9	20.6	78.3
Linezolid	0.5	1	98.8	1.2	98.8	1.2
Minocycline	0.12	0.25	99.4	0.0	99.4	0.6
Moxifloxacin	1	>4	42.2	43.5	33.1	66.9
Tigecycline	0.12	0.25			100.0	0.0
Trimethoprim-sulfamethoxazole	2	>4	58.4	41.6	58.4	20.2
Vancomycin	1	2	100.0	0.0	100.0	0.0
Streptococcus pyogenes (1,699)						
Delafloxacin	0.015	0.03	>99.9	[b]		
Levofloxacin	0.5	1	99.6	0.2	99.6	0.4
Clindamycin	≤0.25	≤0.25	95.1	4.6	95.4	4.6
Erythromycin	≤0.12	4	86.5	12.6	86.5	12.6
Penicillin	≤0.06	≤0.06	100.0		100.0	0.0
Tetracycline	≤0.5	>8	81.5	17.7	80.6	18.5
Tigecycline	0.03	0.06	100.0	[b]	100.0	0.0
Streptococcus agalactiae (827)						
Delafloxacin	0.015	0.03	98.7	0.7 [b]		
Levofloxacin	0.5	1	98.5	1.5	98.5	1.5
Clindamycin	≤0.25	>2	69.0	29.6	70.4	29.6
Erythromycin	≤0.12	>4	52.4	46.0	52.4	46.0
Penicillin	≤0.06	≤0.06	100.0		100.0	0.0
Tetracycline	>8	>8	16.5	83.3	16.3	83.5
Tigecycline	0.06	0.06	100.0	[b]	100.0	0.0
Vancomycin	0.5	0.5	100.0		100.0	0.0
Streptococcus pneumoniae (2,242)						
Delafloxacin	0.015	0.03				
Levofloxacin	1	1	98.7	1.1	98.7	1.3
Azithromycin	0.06	>32	65.4	33.6	64.9	34.6
Ceftaroline	≤0.015	0.12	99.9	[d]	99.6	0.4
Ceftriaxone	≤0.06	1	87.9	3.3 [c]	87.9	0.9
			96.7	0.9 [d]		
Clindamycin	≤0.25	>1	84.5	15.1	84.9	15.1
Erythromycin	≤0.12	>2	63.5	36.0	63.5	36.0
Moxifloxacin	≤0.12	0.25	99.1	0.3	98.9	1.1
Penicillin	≤0.06	2	67.1	10.1 [e]	67.1	32.9 [c]
			67.1	32.9 [f]	67.1	4.1 [d]
			95.9	0.2 [g]		
Tetracycline	≤0.5	>4	78.5	21.2	78.5	21.2
Tigecycline	0.03	0.06	99.5	[b]		
Trimethoprim-sulfamethoxazole	≤0.5	>4	72.8	16.7	78.8	16.7
Penicillin-resistant (>1) *Streptococcus pneumoniae* (227)						
Delafloxacin	0.015	0.03				
Levofloxacin	1	1	97.4	2.2	97.4	2.6
Azithromycin	>32	>32	10.8	87.8	10.8	89.2
Ceftaroline	0.12	0.25	99.1	[d]	95.6	4.4
Ceftriaxone	1	2	9.3	31.7 [c]	9.3	8.8
			68.3	8.8 [d]		
Clindamycin	>1	>1	42.3	56.4	43.6	56.4
Erythromycin	>2	>2	11.5	88.5	11.5	88.5
Moxifloxacin	≤0.12	0.25	97.9	1.1	97.9	2.1
Penicillin	2	4	0.0	100.0 [e]	0.0	40.1 [d]
Tetracycline	>4	>4	33.9	65.6	33.9	65.6
Tigecycline	0.06	0.06	100.0	[b]		
Trimethoprim-sulfamethoxazole	>4	>4	23.8	68.3	29.5	68.3

[a] Criteria as published by CLSI [2017] and EUCAST [2017]
[b] Breakpoints from FDA Package Insert
[c] Using meningitis breakpoints
[d] Using non-meningitis breakpoints
[e] Using oral breakpoints
[f] Using parenteral, meningitis breakpoints
[g] Using parenteral, non-meningitis breakpoints

Table 3 Activity of delafloxacin and comparator agents against Gram-negative bacteria

Antimicrobial agent	MIC_{50}	MIC_{90}	CLSI[a] %S	CLSI[a] %R	EUCAST[a] %S	EUCAST[a] %R
Haemophilus influenzae (969)						
Delafloxacin	≤0.001	0.004				
Levofloxacin	≤0.015	0.03	99.9		98.3	1.7
Azithromycin	0.5	1	99.2		1.1	0.8
Ceftaroline	0.008	0.015	100.0		98.3	1.7
Ciprofloxacin	0.015	0.015	99.7		98.6	1.4
Moxifloxacin	0.03	0.06	99.9		99.4	0.6
Tetracycline	0.5	0.5	99.3	0.6	99.0	0.7
Tigecycline	0.12	0.25	95.7	[b]		
Trimethoprim-sulfamethoxazole	0.12	>4	65.5	31.2	65.5	33.1
Enterobacteriaceae (12,468)						
Delafloxacin	0.12	4	66.7	28.9 [b]		
Levofloxacin	≤0.12	>4	80.8	17.1	76.3	20.9
Amikacin	2	4	98.5	0.8	97.2	1.5
Cefepime	≤0.5	16	86.3	11.0 [c]	84.3	12.2
Ceftazidime	0.25	32	83.8	14.4	79.9	16.2
Ceftriaxone	≤0.06	>8	78.5	20.3	78.5	20.3
Ciprofloxacin	≤0.03	>4	78.6	19.5	74.4	23.3
Meropenem	0.03	0.06	97.4	2.2	97.8	1.5
Minocycline	1	16	81.0	11.8		
Moxifloxacin	≤0.25	>4			66.8	33.2
Tigecycline	0.25	1	98.0	0.1 [b]	92.5	2.0
Trimethoprim-sulfamethoxazole	≤0.5	>4	73.6	26.4	73.6	25.5
Escherichia coli (4,436)						
Delafloxacin	0.06	4	64.8	33.3 [b]		
Levofloxacin	≤0.12	>4	68.9	28.5	67.2	31.6
Amikacin	2	4	99.4	0.1	97.5	0.6
Cefepime	≤0.5	>16	82.9	13.7 [c]	81.4	15.4
Ceftazidime	0.25	16	86.2	11.5	81.1	13.8
Ceftriaxone	≤0.06	>8	80.5	19.3	80.5	19.3
Ciprofloxacin	≤0.03	>4	68.5	31.1	66.1	32.2
Meropenem	≤0.015	0.03	99.7	0.2	99.8	0.1
Minocycline	1	8	86.6	6.8		
Moxifloxacin	≤0.25	>4			61.5	38.5
Tigecycline	0.12	0.25	>99.9	0.0 [b]	>99.9	<0.1
Trimethoprim-sulfamethoxazole	≤0.5	>4	64.1	35.9	64.1	35.0
Klebsiella pneumoniae (2,417)						
Delafloxacin	0.12	>4	64.8	31.5 [b]		
Levofloxacin	≤0.12	>4	78.9	19.2	72.9	22.8
Amikacin	1	4	95.1	2.7	93.1	4.9
Cefepime	≤0.5	>16	72.7	25.0 [c]	71.7	26.3
Ceftazidime	0.25	>32	72.3	25.9	70.2	27.7
Ceftriaxone	≤0.06	>8	70.9	28.8	70.9	28.8
Ciprofloxacin	≤0.03	>4	73.8	22.8	68.0	28.1
Meropenem	0.03	2	89.9	9.0	91.0	6.6
Minocycline	2	16	81.9	11.8		
Moxifloxacin	≤0.25	>4			62.3	37.7
Tigecycline	0.25	1	98.9	0.1 [b]	95.0	1.1
Trimethoprim-sulfamethoxazole	≤0.5	>4	70.3	29.7	70.3	28.7
Pseudomonas aeruginosa (2,181)						
Delafloxacin	0.5	>4	63.6	27.4 [b]		
Levofloxacin	0.5	>4	73.2	20.7	65.0	35.0
Amikacin	4	16	91.4	6.4	87.2	8.6
Cefepime	2	16	82.5	5.6	82.5	17.5
Ceftazidime	2	32	81.6	13.4	81.6	18.4
Ciprofloxacin	0.12	>4	76.7	18.7	72.3	27.7
Colistin	1	2	99.5	0.5	99.5	0.5
Imipenem	1	>8	73.7	22.3	77.7	12.8
Meropenem	0.5	16	75.7	17.8	75.7	11.7
Minocycline	16	>32				
Piperacillin-tazobactam	4	>64	77.3	11.0	77.3	22.7

[a] Criteria as published by CLSI [2017] and EUCAST [2017]
[b] Breakpoints from FDA Package Insert revised 6/2016 for tigecycline and FDA package insert 2017 for delafloxacin
[c] Intermediate interpreted as susceptible-dose dependent

Conclusions

- Delafloxacin was shown to possess broad-spectrum *in vitro* activity against contemporary Gram-positive and -negative bacteria from the US and Europe collected during 2014–2016
- Organisms commonly found in community-acquired pneumonia and ABSSSI were included in the *in vitro* spectrum
- Overall, delafloxacin was more potent *in vitro* against *S. aureus* and CoNS, including methicillin-resistant strains, and against *S. pneumoniae* and β-hemolytic streptococci than levofloxacin and moxifloxacin

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