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In Vitro Activity of Delafloxacin Tested against *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis*

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ABSTRACT

Background: Delafloxacin (DLX) is a broad spectrum fluoroquinolone in late stage clinical development in both oral and intravenous formulations. The in vitro activity of DLX was evaluated against contemporary (USA; 2014) *Streptococcus pneumoniae* (SPN), *Haemophilus influenzae* (HIN), and *Moraxella catarrhalis* (MC) isolates.

Methods: A total of 200 SPN, 200 HIN and 100 MC isolates from a broad geographic distribution across the USA (2014) were tested by MIC against DLX and comparators. Also, a collection of 30 levofloxacin (LEV)-resistant SPN from the USA and Europe were tested. MC were tested in cation-adjusted Mueller-Hinton broth (CA-MHB); SPN in CA-MHB supplemented with lysed horse blood (2.5-5%); and HIN in Haemophilus Test Medium (HTM). Clinical and Laboratory Standards Institute quality control ranges and interpretive criteria were applied.

Results: The DLX MIC_{90} and MIC_{90} for SPN was 0.008 and 0.015 µg/mL, respectively. DLX was 128 x (MIC_{50}) and 64 x (MIC_{90}) more active than LEV. Susceptibility (S) to a number of antimicrobials was compromised for SPN (erythromycin, 52.5% S; trimethoprim-sulfamethoxazole, 75.5% S; tetracycline, 81.0% S; meropenem; 86.0% S). The MIC_{50} and MIC_{90} for DLX and LEV were unchanged for the penicillin-susceptible, -intermediate, or -resistant subsets of SPN. DLX was 16 x more active than the next potent comparator, ceftaroline (MIC_{90}, 0.015 versus 0.25 µg/mL) against penicillin-resistant isolates. DLX (MIC_{50} and MIC_{90}, 0.12 and 0.5 µg/mL) was active against the collection of LEV-resistant SPN. Ceftaroline (MIC_{90}, 0.12 µg/mL; 100.0% S) exhibited the most potent activity against LEV-resistant SPN. For HIN, 24% of which were β-lactamase positive, the MIC_{50} and MIC_{90} values for DLX were ≤0.001 and 0.004 µg/mL. The activities of DLX and LEV against HIN were unaffected by β-lactamase status. Both DLX and LEV were active against MC (95% β-lactamase positive). DLX was the most potent agent tested against MC.

Conclusions: DLX was active against penicillin-resistant, ceftriaxone non-susceptible and LEV-resistant subsets of SPN. The potent in vitro activity of DLX against pathogens frequently associated with community-acquired pneumonia (SPN, HIN and MC), including those that are multidrug-resistant indicate that further study in community-acquired pneumonia is warranted.

INTRODUCTION

Delafloxacin is active against a broad range of Gram-positive and Gram-negative bacteria including anaerobes and atypical bacteria (*Chlamydia* and *Mycoplasma*). It has been shown to be highly active against pathogens which are found in skin and soft tissue infections including fluoroquinolone resistant staphylococci (methicillin-resistant *Staphylococcus aureus* and methicillin-resistant coagulase-negative staphylococci), β-hemolytic streptococci, Enterobacteriaceae, *Pseudomonas aeruginosa*, and anaerobes. Delafloxacin is also active against bacteria associated with respiratory tract infections (hospital and community-acquired respiratory infections) including activity against fluoroquinolone resistant *Streptococcus pneumoniae*.

The aim of this study was to examine the activity profile of delafloxacin against contemporary *S. pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis* clinical isolates collected primarily from United States medical centers during 2014.

MATERIALS AND METHODS

Susceptibility testing: MIC values were determined for *S. pneumoniae* and *H. influenzae* using the reference CLSI broth microdilution method as described in M07-A10 [2015]; broth microdilution for *M. catarrhalis* as described in M45-A2 [2010]. Dry-form panels manufactured by Thermo Fisher Scientific Inc. (Cleveland, Ohio, USA) were used and consisted of three media types; cation-adjusted Mueller-Hinton broth (CA-MHB), Haemophilus Test Medium (HTM), and CA-MHB plus 2.5-5.0% lysed horse blood. Frozen-form panels were produced at JMI Laboratories to test delafloxacin, levofloxacin and ciprofloxacin against *H. influenzae* and *M. catarrhalis* isolates. Interpretive criteria for comparator antimicrobials were those as published by CLSI (M100-S25; 2015) and EUCAST (2015). Quality control was performed per CLSI M07-A10 [2015] and CLSI M100-S25 [2015] recommendations and guidelines and included *S. aureus* ATCC 29213, *S. pneumoniae* ATCC 49619, and *H. influenzae* ATCC 49247.

Organism collection: A total of 200 *S. pneumoniae*, 200 *H. influenzae*, and 100 *M. catarrhalis* from a broad geographic distribution in the USA (2014) were selected. In addition, 30 levofloxacin-resistant *S. pneumoniae* isolates from 2014 (20 from USA, 9 from Europe and one from Australia) were selected.

RESULTS

The MIC distributions for delafloxacin tested against 200 contemporary *S. pneumoniae,* 200 *H. influenzae, and* 100 *M. catarrhalis* (2014; geographically diverse from across the USA census regions) and a collection of 30 levofloxacin-resistant *S. pneumoniae* isolates (20 from USA, 9 from Europe and one from Australia; all from 2014) are located in **Table 1**.

Streptococcus pneumoniae

- The delafloxacin MIC_{50} and MIC_{90} against *S. pneumoniae* were 0.008 and 0.015 µg/mL, respectively (**Table 1**). Delafloxacin was 128 (MIC_{50}) and 64-fold (MIC_{90}) more active than levofloxacin against the 200 *S. pneumoniae* (**Table 2**). The highest delafloxacin MIC was 0.12 µg/mL (**Table 2**). The levofloxacin MIC_{50} and MIC_{90} was 1 and 1 µg/mL, respectively (**Table 2**).
- The MIC_{50} and MIC_{90} for delafloxacin (0.008 and 0.015 µg/mL, respectively) and levofloxacin (1 and 1 µg/mL, respectively) were unchanged for the penicillin-susceptible, -intermediate, or -resistant subsets of *S. pneumoniae* (**Table 1**).
- The activity of delafloxacin and levofloxacin was retained against nine ceftriaxone non-susceptible isolates (**Table 2**).The highest MIC for delafloxacin was 0.015 µg/mL and for levofloxacin was 2 µg/mL (**Table 2**).
- Delafloxacin (MIC_{50} and MIC_{90} 0.12 and 0.5 µg/mL, respectively) was active against the collection of levofloxacin-resistant *S. pneumoniae* (**Tables 1, 2**). MIC values for delafloxacin were increased 16- to 32-fold relative to the general population of *S. pneumoniae* (**Table 1**).
- Delafloxacin was the most active agent tested against *S. pneumoniae* (**Table 2**). It was 8-fold more potent than the next most potent agent, ceftaroline (MIC_{90}, 0.12 µg/mL; 100.0% susceptible), against the collection of contemporary, geographically diverse *S. pneumoniae* isolates (**Table 2**). Susceptibility to a number of antimicrobials was compromised (erythromycin, 52.5% susceptible; trimethoprim-sulfamethoxazole, 75.5% susceptible; tetracycline, 81.0% susceptible; meropenem; 86.0% susceptible).

Penicillin-resistant *S. pneumoniae*

- Delafloxacin was 16-fold more active than the next potent agent, ceftaroline (MIC_{90}, 0.015 versus 0.25 µg/mL) against penicillin-resistant isolates (**Table 2**). Susceptibility for most antimicrobials was generally decreased in this subgroup (penicillin-resistant) compared to the general population with the exception of the fluoroquinolones and ceftaroline. For example, susceptibility to erythromycin, trimethoprim-sulfamethoxazole, and ceftriaxone were 7.7, 15.4 and 53.8%, respectively.

Ceftriaxone non-susceptible *S. pneumoniae*

- The highest MIC for delafloxacin was 16-fold lower than for the most potent comparator moxifloxacin (0.015 versus 0.25 µg/mL; 100.0% susceptible) and 32-fold lower than for ceftaroline (0.015 versus 0.5 µg/mL; 100.0% susceptible) against ceftriaxone non-susceptible *S. pneumoniae* (**Table 2**). The fluoroquinolones (levofloxacin and moxifloxacin) and ceftaroline retained activity (100.0% susceptible), however many of the antimicrobials showed decreased activity compared to the overall population.

Levofloxacin-resistant *S. pneumoniae*

- Ceftaroline (MIC_{90}, 0.12 µg/mL; 100.0% susceptible) demonstrated the most potent activity against levofloxacin-resistant *S. pneumoniae* (**Table 2**). Delafloxacin was the next most active agent (MIC_{90}, 0.5 µg/mL) followed by meropenem (MIC_{90}, 1 µg/mL; 66.7% susceptible) and ceftriaxone (MIC_{90}, 2 µg/mL; 83.3% susceptible). Limited activity with moxifloxacin was noted (MIC_{90}, 4 µg/mL; 20.0% susceptible; **Table 2**).

Haemophilus influenzae

- Delafloxacin and levofloxacin were active against 200 contemporary *H. influenzae* (2014; geographically diverse from across USA census regions), 24% of which were β-lactamase positive (**Table 3**). The MIC_{50} and MIC_{90} values for delafloxacin were ≤0.001 and 0.004 µg/mL, respectively (highest MIC value at 0.25 µg/mL). For levofloxacin the MIC_{50} and MIC_{90} values were 0.015 and 0.03 µg/mL, respectively. However for levofloxacin there were two isolates that were not susceptible (MIC, >2 µg/mL).
- The activities of delafloxacin and levofloxacin against *H. influenzae* were unaffected by β-lactamase status (**Table 1**).
- Delafloxacin was the most potent agent tested against *H. influenzae* (**Table 3**). The MIC_{90} (0.004 µg/mL) for delafloxacin was 4- and 8-fold lower than for ciprofloxacin and levofloxacin, respectively (**Table 3**). Ciprofloxacin and levofloxacin susceptibilities were 99.0% and all isolates were susceptible to ceftaroline, ceftazidime and meropenem. Tetracycline (93.8% compared to 100.0% for β-lactamase-negative isolates) and trimethoprim-sulfamethoxazole (62.5% compared to 65.8%) susceptibilities were lower for the β-lactamase-positive isolates (data not shown).

Moraxella catarrhalis

- Delafloxacin, levofloxacin and ciprofloxacin were active against *M. catarrhalis* (95% β-lactamase positive). However, delafloxacin was 8-fold more active than levofloxacin and ciprofloxacin (**Table 3**).
- Delafloxacin was the most potent agent tested against *M. catarrhalis* (**Table 3**). All isolates were susceptible to amoxicillin-clavulanate, ceftazidime, ciprofloxacin, levofloxacin, and tetracycline.

Table 3. Activity of delafloxacin and comparator antimicrobial agents when tested against isolates of *H. influenzae* and *M. catarrhalis*.

Organism group (no. tested)/ antimicrobial agent	MIC (µg/mL)			%Susceptible / %Resistant	
	MIC_{50}	MIC_{90}	Range	CLSI[a]	EUCAST[a]
Haemophilus influenzae (200)					
Delafloxacin	≤0.001	0.004	≤0.001 — 0.25	-	-
Ciprofloxacin	0.015	0.015	0.004 — >2	99.0/-	98.5/1.5
Levofloxacin	0.015	0.03	0.008 — >2	99.0/-	99.0/1.0
Amoxicillin-clavulanate	≤1	2	≤1 — 8	99.5/0.5	99.0/1.0
Ampicillin	≤0.25	>8	≤0.25 — >8	75.5/23.5	75.5/24.5[b]
Azithromycin	0.5	2	0.12 — >4	99.5/-	1.0/0.5
Ceftaroline	0.008	0.015	0.002 — 0.06	100.0/-	98.5/1.5
Ceftazidime	0.06	0.12	≤0.015 — 0.5	100.0/-	-
Meropenem	≤0.06	0.12	≤0.001 — 0.25	100.0/-	99.5/0.0[c]
				-	100.0/0.0[d]
Tetracycline	0.5	0.5	0.25 — 8	98.5/1.5	98.0/1.5
TMP-SMX[e]	≤0.5	>4	≤0.5 — >4	65.0/29.5	65.0/32.5
M. catarrhalis (100)					
Delafloxacin	0.008	0.008	0.004 — 0.015	-	-
Ciprofloxacin	0.03	0.06	0.015 — 0.06	100.0/-	100.0/0.0
Levofloxacin	0.06	0.06	0.03 — 0.12	100.0/-	100.0/0.0
Amoxicillin-clavulanate	≤1	≤1	≤1 — ≤1	100.0/0.0	100.0/0.0
Ampicillin	1	2	≤0.25 — 8	-/-	-/-
Azithromycin	0.03	0.06	0.015 — 0.5	99.0/-	99.0/0.0
Ceftaroline	0.03	0.12	≤0.008 — 0.25	- /-	- /-
Ceftazidime	0.06	0.12	≤0.015 — 0.25	100.0/-	-/-
Meropenem	≤0.06	≤0.06	≤0.06 — ≤0.06	- /-	100.0/0.0
Penicillin	>0.12	>0.12	≤0.03 — >0.12	- /-	-/-
Tetracycline	≤0.12	0.25	≤0.12 — 0.25	100.0/0.0	100.0/0.0
TMP-SMX[e]	≤0.5	≤0.5	≤0.5 — 2	93.0/0.0	93.0/3.0

a. Criteria as published by CLSI [2015] and EUCAST [2015].
b. BLT positive reported as resistant for penicillins without inhibitors.
c. Using Meningitis breakpoints.
d. Using non-Meningitis breakpoints.
e. TMP-SMX = Trimethoprim-sulfamethoxazole.

Table 1. Cumulative frequency distribution of delafloxacin MIC results when tested against *S. pneumoniae, H. influenzae,* and *M. catarrhalis* isolates.

Organism (no. tested)	No. of organisms (cumulative %) inhibited at delafloxacin MIC in µg/mL of:												
	≤0.001	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	MIC_{50}	MIC_{90}
Streptococcus pneumoniae (200)			20 (10.0)	130 (75.0)	43 (96.5)	5 (99.0)	0 (99.0)	2 (100.0)	--	--	--	0.008	0.015
Pen-S (MIC, ≤0.06 µg/mL; 134)			12 (9.0)	87 (73.9)	30 (96.3)	3 (98.5)	0 (98.5)	2 (100.0)	--	--	--	0.008	0.015
Pen-I (MIC, ≥0.12 and ≤1 µg/mL; 53)			8 (15.1)	35 (81.1)	8 (96.2)	2 100.0)	--	--	--	--	--	0.008	0.015
Pen-R (MIC, ≥2 µg/mL; 13)				8 (61.5)	5 (100.0)	--	--	--	--	--	--	0.008	0.015
CRO-non-S (MIC, ≥2 µg/mL; 9)			1 (11.1)	4 (55.6)	4 (100.0)	--	--	--	--	--	--	--	--
Levofloxacin-R (MIC, ≥8 µg/mL; 30)					5 (16.7)	2 (23.3)	6 (43.3)	6 (63.3)	5 (80.0)	5 (96.7)	1 (100.0)	0.12	0.5
H. influenzae (200)	106 (53.0)	61 (83.5)	26 (96.5)	2 (97.5)	1 (98.0)	2 (99.0)	0 (99.0)	1 (99.5)	1 (100.0)	--	--	≤0.001	0.004
β-lactamase-positive (48)	25 (52.1)	15 (83.3)	6 (95.8)	1 (97.9)	0 (97.9)	1 (100.0)	--	--	--	--	--	≤0.001	0.004
M. catarrhalis (100)			32 (32.0)	64 (96.0)	4 (100.0)	--	--	--	--	--	--	0.008	0.008

Table 2. Activity of delafloxacin and comparator antimicrobial agents when tested against *Streptococcus pneumoniae*.

Organism group (no. tested)/ antimicrobial agent	MIC (µg/mL)			%Susceptible / %Resistant	
	MIC_{50}	MIC_{90}	Range	CLSI[a]	EUCAST[a]
Streptococcus pneumoniae (200)					
Delafloxacin	0.008	0.015	≤0.004 — 0.12	-	-
Levofloxacin	1	1	0.5 — >4	98.5/1.0	98.5/1.5
Amoxicillin-clavulanate	≤1	2	≤1 — >8	94.0/3.5[b]	-
Ceftaroline	≤0.015	0.12	≤0.015 — 0.5	100.0/-[b]	99.5/0.5
Ceftriaxone	≤0.06	1	≤0.06 — 8	83.5/4.5[c]	83.5/1.5
				95.5./1.5[b]	-
Clindamycin	≤0.25	≤0.25	≤0.25 — >2	90.0/10.0	90.0/10.0
Erythromycin	≤0.12	>16	≤0.12 — >16	52.5/45.5	52.5/45.5
Meropenem	≤0.06	0.5	≤0.06 — 2	86.0/3.0	86.0/0.5[c]
				-	100.0/0.0[b]
Moxifloxacin	≤0.12	0.25	≤0.12 — 4	99.0/0.5	98.5/1.5
Penicillin	≤0.06	1	≤0.06 — 8	67.0/6.5[d]	67.0/33.0[c]
				67.0/33.0[e]	67.0/2.5[b]
				97.5/0.5[f]	-
Tetracycline	≤0.5	>8	≤0.5 — >8	81.0/19.0	81.0/19.0
TMP-SMX[g]	≤0.5	4	≤0.5 — >4	75.5/13.5	82.0/13.5
Penicillin-resistant (MIC, ≥2 µg/mL;13)					
Delafloxacin	0.008	0.015	0.008 — 0.015	-	-
Levofloxacin	1	1	0.5 — 1	100.0 /0.0	100.0/0.0
Amoxicillin-clavulanate	8	8	2 — >8	15.4/ 53.8[b]	-
Ceftaroline	0.12	0.25	0.06 — 0.5	100.0 /-[b]	92.3/7.7
Ceftriaxone	1	8	0.5 — 8	7.7/ 46.2[c]	7.7 /23.1
				53.8/ 23.1[b]	-
Clindamycin	≤0.25	>2	≤0.25 — >2	53.8/ 46.2	53.8 /46.2
Erythromycin	>16	>16	≤0.12 — >16	7.7/ 92.3	7.7/92.3
Meropenem	0.5	1	0.5 — 2	0.0/46.2	0.0/ 7.7[c]
				-	100.0/ 0.0[b]
Moxifloxacin	≤0.12	0.25	≤0.12 — 0.25	100.00/0.0	100.0/0.0
Penicillin	2	4	2 — 8	0.0/ 100.0[d]	0.0 /100.0[c]
				0.0/ 100.0[e]	0.0/38.5[b]
				61.5/ 7.7[f]	-
Tetracycline	>8	>8	≤0.5 — >8	30.8/ 69.2	30.8/ 69.2
TMP-SMX[g]	4	>4	≤0.5 — >4	15.4/ 84.6	15.4/84.6
Ceftriaxone-non-susceptible (MIC, ≥2 µg/mL; 9)					
Delafloxacin	-	-	≤0.004 — 0.015	-	-
Levofloxacin	-	-	1 — 2	100.0/0.0	100.0/0.0
Amoxicillin-clavulanate	-	-	≤1 — >8	33.3/55.6[b]	-
Ceftaroline	-	-	0.03 — 0.5	100.0/-[b]	88.9 /11.1
Ceftriaxone	-	-	2 — 8	0.0/100.0[c]	0.0 /33.3
				0.0/33.3[b]	-
Clindamycin	-	-	≤0.25 — >2	66.7/33.3	66.7/33.3
Erythromycin	-	-	1 — >16	0.0/100.0	0.0/100.0
Meropenem	-	-	0.06 — 2	33.3/44.4	33.3/11.1[c]
	-	-	-	-	100.0/0.0[b]
Moxifloxacin	-	-	≤0.12 — 0.25	100.0/0.0	100.0/0.0
Penicillin	-	-	0.25 — 8	0.0/66.7[d]	0.0/100.0[c]
	-	-		0.0/100.0[e]	0.0/44.4[b]
	-	-		55.6/11.1[f]	-
Tetracycline	-	-	≤0.5 — >8	22.2/77.8	22.2/77.8
TMP-SMX[g]	-	-	2 — >4	0.0/77.8	0.0/77.8
Levofloxacin-R (MIC, ≥8 µg/mL; 30)					
Delafloxacin	0.12	0.5	0.015 — 1	-	-
Levofloxacin	>4	>4	>4 — >4	0.0/100.0	0.0/100.0
Amoxicillin-clavulanate	≤1	8	≤1 — 8	66.7/13.3[b]	-/-
Ceftaroline	0.03	0.12	≤0.015 — 0.5	100.0/-[b]	96./3.3
Ceftriaxone	0.12	2	≤0.06 — 8	63.3/16.7[c]	63.3/6.7
				83.3/6.7[b]	-/-
Clindamycin	≤0.25	>2	≤0.25 — >2	76.7/20.0	80.0/20.0
Erythromycin	2	>16	≤0.12 — >16	43.3/56.7	43.3/56.7
Meropenem	0.12	1	≤0.06 — 1	66.7/23.3	66.7/0.0[c]
				- /-	100.0/0.0[b]
Moxifloxacin	2	4	0.25 — >4	20.0 /26.7	20.0/80.0
Penicillin	0.12	4	≤0.06 — 8	43.3/30.0[d]	43.3/56.7[c]
				43.3/56.7[e]	43.3/13.3[b]
				86.7/3.3[f]	-/-
Tetracycline	≤0.5	>8	≤0.5 — >8	50.0/50.0	50.0/50.0
TMP-SMX[g]	≤0.5	>4	≤0.5 — >4	50.0/46.7	53.3/46.7

a. Criteria as published by CLSI [2015] and EUCAST [2015].
b. Using non-Meningitis breakpoints.
c. Using Meningitis breakpoints.
d. Using Oral breakpoints.
e. Using Parenteral, Meningitis breakpoints.
f. Using Parenteral, non-Meningitis breakpoints.
g. TMP-SMX = Trimethoprim-sulfamethoxazole.

CONCLUSIONS

- Delafloxacin was the most potent compound tested against *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. It was 64- to 128-fold more potent than levofloxacin against *S. pneumoniae* and 8-fold more potent against *H. influenzae* and *M. catarrhalis*.
- Delafloxacin was active against penicillin-resistant, ceftriaxone non-susceptible and levofloxacin-resistant subsets of *S. pneumoniae*.
- Delafloxacin activity was not affected by β-lactamase status for *H. influenzae* and *M. catarrhalis*.
- The potent activity of delafloxacin, particularly against multi-drug resistant pathogens, demonstrates that further clinical study in community-acquired pneumonia are warranted.

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