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

Robert K. Flamm, Paul R. Rhomberg, Michael D. Huband, David J. Farrell

JMI Laboratories, North Liberty, Iowa, USA

Delafloxacin, an investigational anionic fluoroquinolone, is active against a broad range of Gram-positive and Gram-negative bacteria. In this study, 200 *Streptococcus pneumoniae* (plus 30 levofloxacin-resistant isolates), 200 *Haemophilus influenzae*, and 100 *Moraxella catarrhalis* isolates selected primarily from the United States (2014) were tested against delafloxacin and comparator agents. Delafloxacin was the most potent agent tested. MIC_{50} and MIC_{90} values against all *S. pneumoniae* isolates were 0.008 and 0.015 μg/ml. Delafloxacin susceptibility was not affected by β-lactamase status against *H. influenzae* and *M. catarrhalis*.

Delafloxacin is an investigational anionic fluoroquinolone antibacterial currently in phase III development for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) (NCT01811732 and NCT01984684). Unlike other quinolones, which usually have a binding preference for DNA gyrase or topoisomerase IV, delafloxacin is equally potent against both enzymes (1). This dual targeting is believed to help reduce the selection of resistant mutants *in vitro* (1). Additionally, the anionic structure of delafloxacin may enhance its potency in acidic environments, which may be characteristic of the milieu at an infection site (2).

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Delafloxacin is active against a broad range of Gram-positive and Gram-negative bacteria, including anaerobes and atypical bacteria (*Chlamydia* and *Mycoplasma*) (1, 3–8). It is highly active against pathogens that are found in skin and soft tissue infections, including fluoroquinolone-resistant staphylococci, methicillin-resistant *Staphylococcus aureus*, methicillin-resistant coagulase-negative staphylococci, β-hemolytic streptococci, enteric bacteria, *Pseudomonas aeruginosa*, and anaerobes (1, 3, 5, 7). Delafloxacin is also active against bacteria associated with respiratory tract infections (RTI; hospital and community acquired), including activity against fluoroquinolone-resistant *Streptococcus pneumoniae* (1, 3–6, 8).

Two hundred *S. pneumoniae* isolates (plus 30 isolates selected for levofloxacin resistance), 200 *Haemophilus influenzae* isolates, and 100 *Moraxella catarrhalis* isolates were selected for this study, primarily from United States medical centers from the SENTRY surveillance platform. These isolates were collected from January through December 2014. MIC values were determined for *S. pneumoniae* and *H. influenzae* according to the broth microdilution method described in CLSI document M07-A10 (9); broth microdilution methods used for *M. catarrhalis* were as described in CLSI document M45-Ed3 (10). Dry-form panels (Thermo Fisher Scientific, Cleveland, OH, USA) to test *S. pneumoniae* and frozen-form panels (JMI Laboratories) to test delafloxacin, levofloxacin, and ciprofloxacin against *H. influenzae* and *M. catarrhalis* isolates were used and consisted of three media types: cation-adjusted Mueller-Hinton broth (CA-MHB), CA-MHB plus 2.5% to 5.0% lysed horse blood, and *Haemophilus* test medium. Quality control ranges and interpretive criteria used for the comparator compounds were those published in CLSI document M100-S26 and by EUCAST (11, 12).

Delafloxacin was 128-fold (MIC_{50}) and 64-fold (MIC_{90}) more active than levofloxacin against all *S. pneumoniae* isolates (Table 1). The delafloxacin MIC_{50} and MIC_{90} values for *S. pneumoniae* were 0.008 and 0.015 μg/ml, respectively, with the highest MIC value at 0.12 μg/ml (Table 1). The MIC_{50} and MIC_{90} values for delafloxacin (0.008 and 0.015 μg/ml) and levofloxacin (1 and 1 μg/ml) were unchanged for multidrug-resistant (MDR; nonsusceptible to at least two of penicillin, ceftriaxone, levofloxacin, tetracycline, trimethoprim-sulfamethoxazole, and erythromycin) isolates and the penicillin-susceptible, -intermediate, and -resistant subsets of *S. pneumoniae* (Table 1). Delafloxacin and levofloxacin retained activity against nine ceftriaxone-nonsusceptible isolates (Table 1). MIC values for delafloxacin were increased 16- to 32-fold (MIC_{50} and MIC_{90}, 0.12 and 0.5 μg/ml) relative to the general population of *S. pneumoniae* when tested against levofloxacin-resistant *S. pneumoniae*.

Delafloxacin was 8-fold more potent than the next most potent agent, i.e., ceftaroline (MIC_{90}, 0.12 μg/ml; 100.0% susceptible), against *S. pneumoniae* (Table 1). Susceptibilities to erythromycin (52.5% susceptible), trimethoprim-sulfamethoxazole (75.5% susceptible), tetracycline (81.0% susceptible), and meropenem (86.0% susceptible) were compromised (Table 1). Against penicillin-resistant isolates, delafloxacin was 16-fold more active than the next potent comparator, i.e., ceftaroline (MIC_{90}, 0.015 versus 0.25 μg/ml) (Table 1). Susceptibilities for most antimicrobials

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Address correspondence to Robert K. Flamm, robert-flamm@jmilabs.com.

TABLE 1 Activity of delafloxacin and comparator antimicrobial agents tested against isolates of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*

Species (no. isolates) and antimicrobial	MIC (μg/ml)			Result (%) using criteria from[a]:			
				CLSI		EUCAST	
	MIC_{50}	MIC_{90}	Range	S	R	S	R
S. pneumoniae (200)							
Delafloxacin	0.008	0.015	≤0.004 to 0.12				
Levofloxacin	1	1	0.5 to >4	98.5	1.0	98.5	1.5
Amoxicillin-clavulanate	≤1	2	≤1 to >8	94.0	3.5[b]		
Moxifloxacin	≤0.12	0.25	≤0.12 to 4	99.0	0.5	98.5	1.5
Ceftaroline	≤0.015	0.12	≤0.015 to 0.5	100.0	[b]	99.5	0.5
Ceftriaxone	≤0.06	1	≤0.06 to 8	83.5	4.5[c]	83.5	1.5
				95.5	1.5[b]		
Clindamycin	≤0.25	≤0.25	≤0.25 to >2	90.0	10.0	90.0	10.0
Erythromycin	≤0.12	>16	≤0.12 to >16	52.5	45.5	52.5	45.5
Meropenem	≤0.06	0.5	≤0.06 to 2	86.0	3.0	86.0	0.5[c]
						100.0	0.0[b]
Penicillin	≤0.06	1	≤0.06 to 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 to >8	81.0	19.0	81.0	19.0
Trimethoprim-sulfamethoxazole	≤0.5	4	≤0.5 to >4	75.5	13.5	82.0	13.5
S. pneumoniae (MDR) (82)							
Delafloxacin	0.008	0.015	≤0.004 to 0.12				
Levofloxacin	1	1	0.5 to >4	97.6	1.2	97.6	2.4
Moxifloxacin	≤0.12	0.25	≤0.12 to 4	98.8	1.2	98.8	1.2
Amoxicillin-Clavulanate	≤1	4	≤1 to >8	85.4	8.5[b]		
Ceftaroline	0.06	0.12	≤0.015 to 0.5	100.0	[b]	98.8	1.2
Ceftriaxone	0.5	2	≤0.06 to 8	62.2	11.0[c]	62.2	3.7
				89.0	3.7[b]		
Clindamycin	≤0.25	>2	≤0.25 to >2	75.6	24.4	75.6	24.4
Erythromycin	8	>16	≤0.12 to >16	8.5	87.8	8.5	87.8
Meropenem	0.12	0.5	≤0.06 to 2	67.1	7.3	67.1	1.2[c]
						100.0	0.0[b]
Penicillin	0.25	2	≤0.06 to 8	28.0	15.9[d]	28.0	72.0[c]
				28.0	72.0[e]	28.0	6.1[b]
				93.9	1.2[f]		
Tetracycline	≤0.5	>8	≤0.5 to >8	53.7	46.3	53.7	46.3
Trimethoprim-sulfamethoxazole	1	>4	≤0.5 to >4	46.3	28.0	61.0	28.0
S. pneumoniae penicillin resistant (>1 μg/ml) (13)							
Delafloxacin	0.008	0.015	0.008 to 0.015				
Levofloxacin	1	1	0.5 to 1	100.0	0.0	100.0	0.0
Moxifloxacin	≤0.12	0.25	≤0.12 to 0.25	100.0	0.0	100.0	0.0
Amoxicillin-clavulanate	8	8	2 to >8	15.4	53.8[b]		
Ceftaroline	0.12	0.25	0.06 to 0.5	100.0	[b]	92.3	7.7
Ceftriaxone	1	8	0.5 to 8	7.7	46.2[c]	7.7	23.1
				53.8	23.1[b]		
Clindamycin	≤0.25	>2	≤0.25 to >2	53.8	46.2	53.8	46.2
Erythromycin	>16	>16	≤0.12 to >16	7.7	92.3	7.7	92.3
Meropenem	0.5	1	0.5 to 2	0.0	46.2	0.0	7.7[c]
						100.0	0.0[b]
Penicillin	2	4	2 to 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 to >8	30.8	69.2	30.8	69.2
Trimethoprim-sulfamethoxazole	4	>4	≤0.5 to >4	15.4	84.6	15.4	84.6
S. pneumoniae ceftriaxone nonsusceptible (>1 μg/ml) (9)							
Delafloxacin			≤0.004 to 0.015				
Levofloxacin			1 to 2	100.0	0.0	100.0	0.0
Moxifloxacin			≤0.12 to 0.25	100.0	0.0	100.0	0.0
Amoxicillin-clavulanate			≤1 to >8	33.3	55.6[b]		
Ceftaroline			0.03 to 0.5	100.0	[b]	88.9	11.1
Ceftriaxone			2 to 8	0.0	100.0[c]	0.0	33.3
				0.0	33.3[b]		
Clindamycin			≤0.25 to >2	66.7	33.3	66.7	33.3
Erythromycin			1 to >16	0.0	100.0	0.0	100.0

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TABLE 1 (Continued)

Species (no. isolates) and antimicrobial	MIC (μg/ml)			Result (%) using criteria from[a]:			
				CLSI		EUCAST	
	MIC_{50}	MIC_{90}	Range	S	R	S	R
Meropenem			0.06 to 2	33.3	44.4	33.3	11.1[c]
						100.0	0.0[b]
Penicillin			0.25 to 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 to >8	22.2	77.8	22.2	77.8
Trimethoprim-sulfamethoxazole			2 to >4	0.0	77.8	0.0	77.8
S. pneumoniae levofloxacin-resistant (>4 μg/ml) (30)							
Delafloxacin	0.12	0.5	0.015 to 1				
Levofloxacin	>4	>4	>4 to >4	0.0	100.0	0.0	100.0
Moxifloxacin	2	4	0.25 to >4	20.0	26.7	20.0	80.0
Amoxicillin-clavulanate	≤1	8	≤1 to 8	66.7	13.3[b]		
Ceftaroline	0.03	0.12	≤0.015 to 0.5	100.0	[b]	96.7	3.3
Ceftriaxone	0.12	2	≤0.06 to 8	63.3	16.7[c]	63.3	6.7
				83.3	6.7[b]		
Clindamycin	≤0.25	>2	≤0.25 to >2	76.7	20.0	80.0	20.0
Erythromycin	2	>16	≤0.12 to >16	43.3	56.7	43.3	56.7
Meropenem	0.12	1	≤0.06 to 1	66.7	23.3	66.7	0.0[c]
						100.0	0.0[b]
Penicillin	0.12	4	≤0.06 to 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 to >8	50.0	50.0	50.0	50.0
Trimethoprim-sulfamethoxazole	≤0.5	>4	≤0.5 to >4	50.0	46.7	53.3	46.7
H. influenzae (200)							
Delafloxacin	≤0.001	0.004	≤0.001 to 0.25				
Ciprofloxacin	0.015	0.015	0.004 to >2	99.0		98.5	1.5
Levofloxacin	0.015	0.03	0.008 to >2	99.0		99.0	1.0
Amoxicillin-clavulanate	≤1	2	≤1 to 8	99.5	0.5	99.0	1.0
Ampicillin	≤0.25	>8	≤0.25 to >8	75.5	23.5	75.5	24.5
Azithromycin	0.5	2	0.12 to >4	99.5		1.0	0.5
Ceftaroline	0.008	0.015	0.002 to 0.06	100.0		98.5	1.5
Ceftazidime	0.06	0.12	≤0.015 to 0.5	100.0			
Meropenem	≤0.06	0.12	≤0.06 to 0.5	100.0		99.5	0.0[c]
						100.0	0.0[b]
Tetracycline	0.5	0.5	0.25 to 8	98.5	1.5	98.0	1.5
Trimethoprim-sulfamethoxazole	≤0.5	>4	≤0.5 to >4	65.0	29.5	65.0	32.5
M. catarrhalis (100)							
Delafloxacin	0.008	0.008	0.004 to 0.015				
Ciprofloxacin	0.03	0.06	0.015 to 0.06	100.0		100.0	0.0
Levofloxacin	0.06	0.06	0.03 to 0.12	100.0		100.0	0.0
Amoxicillin-clavulanate	≤1	≤1	≤1 to ≤1	100.0	0.0	100.0	0.0
Ampicillin	1	2	≤0.25 to 8				
Azithromycin	0.03	0.06	0.015 to 0.5	99.0		99.0	0.0
Ceftaroline	0.03	0.12	≤0.008 to 0.25				
Ceftazidime	0.06	0.12	≤0.015 to 0.25	100.0			
Meropenem	≤0.06	≤0.06	≤0.06 to ≤0.06			100.0	0.0
Penicillin	>0.12	>0.12	≤0.03 to >0.12				
Tetracycline	≤0.12	0.25	≤0.12 to 0.25	100.0	0.0	100.0	0.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 to 2	93.0	0.0	93.0	3.0

[a] Criteria as published by CLSI (11) and EUCAST (12). S, susceptible; R, resistant; intermediate percentages are not presented.
[b] Using nonmeningitis breakpoints.
[c] Using meningitis breakpoints.
[d] Using oral breakpoints.
[e] Using parenteral meningitis breakpoints.
[f] Using parenteral nonmeningitis breakpoints.

were generally decreased among penicillin-resistant isolates compared to those of the general population, with the exception of the fluoroquinolones and ceftaroline. For example, susceptibilities to erythromycin, trimethoprim-sulfamethoxazole, and ceftriaxone were 7.7%, 15.4%, and 53.8%, respectively (Table 1). The highest MIC for delafloxacin was 16-fold lower than that for the most potent comparator, i.e., moxifloxacin (0.015 versus 0.25 μg/ml), and 32-fold lower than that for ceftaroline (0.015 versus 0.5 μg/

ml) against ceftriaxone-nonsusceptible *S. pneumoniae* (Table 1). The fluoroquinolones (levofloxacin and moxifloxacin) and ceftaroline retained activity (100.0% susceptible) against ceftriaxone-nonsusceptible *S. pneumoniae*; however, many of the other antimicrobials showed decreased activity compared to the normal population. Ceftaroline (MIC_{90}, 0.12 μg/ml; 100.0% susceptible) demonstrated the most potent activity against levofloxacin-resistant *S. pneumoniae*, followed by delafloxacin (MIC_{90}, 0.5 μg/ml), 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).

The MIC_{50} and MIC_{90} values for delafloxacin against *H. influenzae* were ≤0.001 and 0.004 μg/ml (highest MIC value at 0.25 μg/ml) (Table 1). For levofloxacin, the MIC_{50} and MIC_{90} values were 0.015 and 0.03 μg/ml; however, two isolates were not susceptible (MIC, >2 μg/ml) (Table 1). The activities of delafloxacin and levofloxacin against *H. influenzae* were unaffected by β-lactamase status (data not shown). Both delafloxacin and levofloxacin were active against *M. catarrhalis*, although delafloxacin was 8-fold more active than levofloxacin (Table 1).

Delafloxacin was the most potent agent tested against *H. influenzae* (Table 1). The MIC_{90} (0.004 μg/ml) was 4-fold and 8-fold lower than those for ciprofloxacin and levofloxacin, respectively (Table 1). Ciprofloxacin and levofloxacin susceptibilities were 99.0%, and all isolates were susceptible to ceftaroline, ceftazidime, and meropenem (Table 1). Tetracycline (93.8% versus 100.0% for β-lactamase-negative isolates) and trimethoprim-sulfamethoxazole (62.5% versus 65.8%) susceptibilities were lower for the β-lactamase-positive isolates (data not shown). Delafloxacin was the most potent agent tested against *M. catarrhalis*, exhibiting an MIC_{90} (0.008 μg/ml) that was 8-fold lower than those for ciprofloxacin and levofloxacin (Table 1). All isolates were susceptible to amoxicillin-clavulanate, ceftazidime, ciprofloxacin, levofloxacin, and tetracycline (Table 1).

In a bacterial respiratory surveillance program conducted from 1997 to 2002 throughout Canada (CROSS), the delafloxacin MIC_{50} and MIC_{90} values were 0.008 and 0.015 μg/ml when tested against 6,991 isolates of *S. pneumoniae* (13). These values were similar for delafloxacin when it was tested against 389 penicillin-resistant strains (MIC_{50} and MIC_{90}, 0.015 and 0.015 μg/ml) (13). The MIC_{50} and MIC_{90} values for delafloxacin tested against 200 contemporary *S. pneumoniae* isolates from the United States in this study were also 0.008 and 0.015 μg/ml, respectively, and the MIC_{90} for delafloxacin tested against penicillin-resistant isolates matched that of the CROSS study. This indicates that delafloxacin maintained its potency despite the selective pressure of fluoroquinolone use in the intervening decade. In a study of the comparative activity of delafloxacin against Gram-positive and Gram-negative pathogens, Harnett et al. (5) demonstrated that the MIC_{50} and MIC_{90} values for delafloxacin tested against *H. influenzae* were both 0.001 μg/ml, and the MIC_{50} and MIC_{90} values for delafloxacin against *M. catarrhalis* were both 0.008 μg/ml. The data from our current study are consistent with the highly potent nature of the activity of delafloxacin, with MIC_{50} and MIC_{90} values of ≤0.001 and 0.004 μg/ml against *H. influenzae* and ≤0.008 and ≤0.008 μg/ml against *M. catarrhalis*.

Overall, delafloxacin was the most potent compound tested against *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* in our study. It was active against penicillin-resistant, ceftriaxone-nonsusceptible, and levofloxacin-resistant subsets of *S. pneumoniae*. Although delafloxacin demonstrated potent activity against levofloxacin-resistant organisms, MIC values were increased compared to those in wild-type organisms. The MIC_{50} and MIC_{90} values were 0.008 and 0.015 μg/ml against the collection of 200 *S. pneumoniae* and 0.12 and 0.5 μg/ml against 30 levofloxacin-resistant isolates, which is a 16- to 32-fold increase. This level of cross-resistance suggests some overlap in the binding targets of DNA gyrase and topoisomerase IV. The potent activity of delafloxacin against pathogens frequently associated with community-acquired pneumonia (*S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*), including those that are MDR, indicates that further study in community-acquired bacterial pneumonia is warranted.

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