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In vitro Evaluation of Delafloxacin Activity When Tested against Contemporary European Community-Acquired Bacterial Respiratory Tract Infection Isolates (2014–2017): Results from the SENTRY Antimicrobial Surveillance Program

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Introduction

- Delafloxacin is a broad-spectrum fluoroquinolone antibacterial that has completed clinical development (oral and intravenous formulations) for acute bacterial skin and skin structure infections
- The delafloxacin new drug application was approved by the US Food and Drug Administration in 2017 to treat acute bacterial skin and skin structure infections
  - Delafloxacin is in phase 3 clinical development for community-acquired bacterial pneumonia
- In this study, *in vitro* susceptibility results for delafloxacin and comparator agents were determined for clinical isolates from community-acquired respiratory tract infections (CARTI) collected from 36 medical centres in Europe participating in the SENTRY Antimicrobial Surveillance Program from 2014 to 2017

Materials and Methods

- A total of 2,538 isolates that included 1,375 *Streptococcus pneumoniae*, 690 *Haemophilus influenzae*, and 450 *Moraxella catarrhalis* were collected from 2014 to 2017
  - Only 1 isolate/patient/infection episode was included
  - Isolate identifications were confirmed at JMI Laboratories
- Susceptibility testing was performed according to CLSI reference broth microdilution methodology, and results were interpreted per CLSI and EUCAST (2018) criteria
- Other antimicrobials tested included levofloxacin, moxifloxacin, amoxicillin-clavulanic acid, ceftaroline, ceftriaxone, clindamycin, erythromycin, linezolid, meropenem, tetracycline, trimethoprim-sulfamethoxazole, and penicillin
  - *Streptococcus pneumoniae* isolates were categorized by penicillin MIC using EUCAST non-meningitis breakpoints of susceptible <0.12 mg/L, intermediate 0.12-1.0 mg/L, and resistant >1.0 mg/L
  - Fluoroquinolone-resistant *S. pneumoniae* isolates were categorized by a levofloxacin MIC >2.0 mg/L
- β-lactamase production for *H. influenzae* and *M. catarrhalis* was determined by the nitrocefin disk test

Results

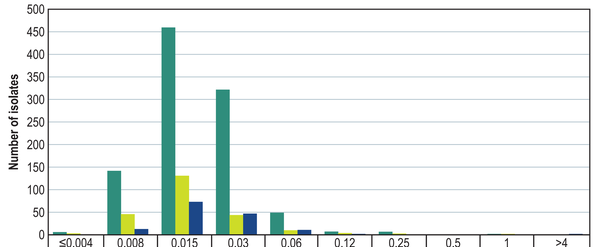
- Delafloxacin demonstrated potent *in vitro* activity against 1,375 *S. pneumoniae* ($MIC_{50/90}$ 0.015/0.03 mg/L) and was more active than levofloxacin ($MIC_{50/90}$ 1/2 mg/L) or moxifloxacin ($MIC_{50/90}$ ≤0.12/0.25 mg/L), as shown in Tables 1 and 2
  - Delafloxacin had the lowest MIC_{90} of the agents tested
- Activity for delafloxacin remained the same for 238 penicillin-intermediate and 144 penicillin-resistant isolates (Figure 1)
- For 32 levofloxacin-resistant *S. pneumoniae* (levofloxacin MIC >2 mg/L) isolates, the delafloxacin $MIC_{50/90}$ values were 0.12/0.25 mg/L with 96.9% of the isolates having delafloxacin MICs ≤1 mg/L (Figure 2)
- For 690 *H. influenzae*, delafloxacin was extremely potent with $MIC_{50/90}$ values of ≤0.001/0.002 mg/L; levofloxacin $MIC_{50/90}$ were ≤0.015/0.03 mg/L, and moxifloxacin $MIC_{50/90}$ were 0.03/0.03 mg/L (Tables 1 and 2)
  - Delafloxacin had the lowest MIC_{90} of the agents tested
- For 450 *M. catarrhalis*, the delafloxacin $MIC_{50/90}$ were 0.004/0.008 mg/L and the $MIC_{50/90}$ values for levofloxacin and moxifloxacin were 0.06/0.06 mg/L and 0.06/0.06 mg/L, respectively (Tables 1 and 2)
  - Delafloxacin had the lowest MIC_{90} of the agents tested

Table 1 Delafloxacin, moxifloxacin, and levofloxacin MIC distributions against the isolates in this study

Organism/ organism group	Drug	Total	Number (%) at MIC in mg/L												MIC$_{50}$ (mg/L)	MIC$_{90}$ (mg/L)
			0.001	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	>*		
Streptococcus pneumoniae	Delafloxacin	1,375			18 (1.3)	198 (15.7)	661 (63.8)	410 (93.6)	67 (98.5)	10 (99.2)	8 (99.8)	0 (99.8)	2 (99.9)	0 (99.9)	0 (99.9)	1 (100.0)	0.015	0.03
Streptococcus pneumoniae	Levofloxacin	1,375								0 (0.0)	1 (0.1)	168 (12.3)	1,030 (87.2)	144 (97.7)	7 (98.2)	25 (100.0)	1	2
Streptococcus pneumoniae	Moxifloxacin	1,255								1,002 (79.8)	224 (97.7)	11 (98.6)	0 (98.6)	12 (99.5)	3 (99.8)	3 (100.0)	≤0.12	0.25
Haemophilus influenzae	Delafloxacin	690	548 (79.4)	101 (94.1)	24 (97.5)	9 (98.8)	4 (99.4)	0 (99.4)	2 (99.7)	0 (99.7)	1 (99.9)					1 (100.0)	≤0.001	0.002
Haemophilus influenzae	Levofloxacin	690					447 (64.8)	231 (98.3)	6 (99.1)	1 (99.3)	2 (99.6)	0 (99.6)	0 (99.6)	1 (99.7)		2 (100.0)	≤0.015	0.03
Haemophilus influenzae	Moxifloxacin	606				7 (1.2)	227 (38.6)	327 (92.6)	37 (98.7)	5 (99.5)	0 (99.5)	0 (99.5)	0 (99.5)			3 (100.0)	0.03	0.03
Moraxella catarrhalis	Delafloxacin	450	6 (1.3)	61 (14.9)	217 (63.1)	144 (95.1)	18 (99.1)	2 (99.6)	1 (99.8)	1 (100.0)							0.004	0.008
Moraxella catarrhalis	Levofloxacin	450					6 (1.3)	215 (49.1)	222 (98.4)	2 (98.9)	0 (98.9)	1 (99.1)	3 (99.8)	1 (100.0)			0.06	0.06
Moraxella catarrhalis	Moxifloxacin	359				1 (0.3)	0 (0.3)	77 (21.7)	273 (97.8)	4 (98.9)	2 (99.4)	1 (99.7)	1 (100.0)				0.06	0.06

*Greater than highest dilution tested

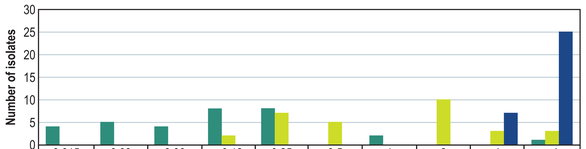
Figure 1 Delafloxacin MIC distribution when tested against *S. pneumoniae* grouped by penicillin MIC (non-meningitis breakpoints[a])



	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	>4
Penicillin MIC <0.12 mg/L	11	141	459	321	48	6	6	0	1	0
Penicillin MIC 0.12-1 mg/L	5	45	130	43	9	3	2	0	1	0
Penicillin MIC >1 mg/L	2	12	72	46	10	1	0	0	0	1

[a] EUCAST (2018)

Figure 2 MIC distribution of delafloxacin, moxifloxacin, and levofloxacin against 32 levofloxacin-resistant *S. pneumoniae*



	0.015	0.03	0.06	≤0.12	0.25	0.5	1	2	4	>4
Delafloxacin	4	5	4	8	8	0	2	0	0	1
Moxifloxacin				2	7	5	0	10	3	3
Levofloxacin									7	25

Conclusions

- Delafloxacin demonstrated extremely potent *in vitro* antibacterial activity against CARTI pathogens that included *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*
  - Delafloxacin was very active against penicillin-intermediate (penicillin MIC 0.12-1.0 mg/L) and penicillin-resistant (penicillin MIC >1.0 mg/L) *S. pneumoniae*
  - Delafloxacin inhibited all but 1 levofloxacin-nonsusceptible *S. pneumoniae* isolate at an MIC ≤1.0 mg/L
- These data support the continued clinical development of delafloxacin as a potential treatment for community-acquired pneumonia

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Table 2 Antimicrobial activity of delafloxacin and comparator agents tested against CARTI isolates

Antimicrobial agent	MIC$_{50}$ (mg/L)	MIC$_{90}$ (mg/L)	Range (mg/L)	CLSI[a]			EUCAST[a]		
				%S	%I	%R	%S	%I	%R
Streptococcus pneumoniae (n=1,375)									
Delafloxacin	0.015	0.03	≤0.004 to >4						
Levofloxacin	1	2	0.25 to >4	97.7	0.5	1.8	97.7		2.3
Moxifloxacin	≤0.12	0.25	≤0.12 to >4	98.6	1.0	0.5	98.6		1.4
Amoxicillin-clavulanic acid	≤1	2	≤1 to >4	94.4	1.8	3.8			
Ceftaroline	≤0.015	0.12	≤0.015 to >1	99.9		[b]	99.8		0.2
Ceftriaxone	≤0.06	1	≤0.06 to >2	88.2	8.2	3.6 [c]	88.2	11.2	0.6
				96.4	3.1	0.6 [b]			
Clindamycin	≤0.25	>1	≤0.25 to >1	82.8	0.5	16.7	83.3		16.7
Erythromycin	≤0.12	>2	≤0.12 to >2	76.0	0.2	23.8	76.0	0.2	23.8
Linezolid	1	2	0.25 to 2	100.0			100.0	0.0	0.0
Meropenem	≤0.015	0.5	≤0.015 to >1	87.4	7.1	5.5	87.4	12.4	0.2 [c]
							100.0		0.0 [b]
Penicillin	≤0.06	2	≤0.06 to >4	72.2	17.3	10.5 [d]	72.2		27.8 [c]
				72.2		27.8 [e]	72.2	23.0	4.8 [b]
				95.2	4.7	0.1 [f]			
Tetracycline	≤0.5	>4	≤0.5 to >4	77.9	0.3	21.8	77.9	0.3	21.8
Trimethoprim-sulfamethoxazole	≤0.5	>4	≤0.5 to >4	74.0	8.4	17.6	78.7	3.7	17.6
Haemophilus influenzae (n=690)									
Delafloxacin	≤0.001	0.002	≤0.001 to >0.25						
Levofloxacin	≤0.015	0.03	≤0.015 to >2	99.7			99.1		0.9
Ciprofloxacin	0.015	0.015	≤0.008 to >1	99.6			99.3		0.7
Moxifloxacin	0.03	0.03	≤0.008 to >1	99.5			99.5		0.5
Amoxicillin-clavulanic acid	0.5	2	≤0.12 to 8	99.9		0.1	94.9		5.1
Ampicillin	0.5	>8	≤0.12 to >8	73.5	5.9	20.6	73.5		26.5
Azithromycin	1	1	≤0.12 to >8	98.8			98.8 [g]		
Ceftaroline	0.008	0.03	≤0.004 to 0.5	100.0			98.5		1.5
Ceftazidime	0.06	0.12	≤0.015 to 0.25	100.0					
Ceftriaxone	≤0.015	≤0.015	≤0.015 to 0.12	100.0			100.0		0.0
Clarithromycin	8	16	≤0.12 to >16	88.8	9.7	1.4	100.0 [g]		
Meropenem	0.06	0.12	≤0.008 to 0.5	100.0			99.6	0.4	0.0 [c]
							100.0		0.0 [b]
Tetracycline	0.5	1	0.25 to >8	99.3	0.0	0.7	99.0	0.3	0.7
Trimethoprim-sulfamethoxazole	0.12	>4	≤0.06 to >4	62.2	6.1	31.7	62.2	2.9	34.9
Moraxella catarrhalis (n=450)									
Delafloxacin	0.004	0.008	0.001 to 0.12						
Levofloxacin	0.06	0.06	≤0.015 to 2	100.0			98.9		1.1
Moxifloxacin	0.06	0.06	≤0.008 to 1				99.4		0.6
Amoxicillin-clavulanic acid	≤0.25	≤0.25	≤0.25 to 0.5	100.0		0.0	100.0		0.0
Azithromycin	0.015	0.03	0.008 to 0.06	100.0			100.0	0.0	0.0
Ceftaroline	0.06	0.25	≤0.008 to 1						
Ceftazidime	0.06	0.25	≤0.015 to 0.5	100.0					
Ceftriaxone	0.25	0.5	≤0.015 to 2	100.0			99.8	0.2	0.0
Clarithromycin	≤0.12	0.25	≤0.12 to 0.5	100.0			99.8	0.2	0.0
Meropenem	≤0.015	≤0.015	≤0.015 to ≤0.015				100.0		0.0
Penicillin	>4	>4	≤0.03 to >4						
Tetracycline	0.25	0.5	≤0.06 to >8	99.6	0.0	0.4	99.6	0.0	0.4
Trimethoprim-sulfamethoxazole	0.12	0.25	≤0.06 to 4	97.1	2.4	0.4	97.1	1.6	1.3

[a] Criteria as published by CLSI 2018 and EUCAST 2018.
[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] Percentage of wild type based on ECV. EUCAST version 8.0 2018.

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