Activity of Delafloxacin against Multi-Drug-Resistant **Fastidious Respiratory Pathogens from European** Medical Centers (2014–2019)

Dee Shortridge, Jennifer M. Streit, Michael D. Huband, Robert K. Flamm JMI Laboratories, North Liberty, IA, USA

Introduction

- Delafloxacin is an anionic fluoroquinolone approved in the United States and Europe for the treatment of acute bacterial skin and skin structure infections
- Delafloxacin recently was approved in the United States for treatment of community-acquired bacterial pneumonia (CABP).
- This study examines the *in vitro* susceptibilities of delafloxacin and comparator agents against recent European isolates of Streptococcus pneumoniae, Haemophilus influenzae, H. parainfluenzae, and Moraxella catarrhalis.
- This study also analyzed the delafloxacin susceptibility of isolates resistant to current first-line therapies: Erythromycin-resistant S. pneumoniae, multi-drug resistant S. pneumoniae, and β-lactamase positive *H. influenzae*.

Materials and Methods

- A total of 2,835 S. pneumoniae, 1,484 H. influenzae, 959 M. catarrhalis, and 20 H. parainfluenzae isolates were collected from community-acquired respiratory tract infections (CA-RTI) from European hospitals between 2014 and 2019. Sites included only 1 isolate/patient/infection episode.
- JMI Laboratories confirmed isolate identifications using biochemical and/ or molecular methods as needed. Susceptibility testing was performed by broth microdilution methodology according to CLSI (CLSI M07, 2018).
- Where applicable, CLSI/ FDA and EUCAST v. 10.0 (2020) breakpoints were used.
- Delafloxacin has FDA but not EUCAST breakpoints for CABP organisms S. pneumoniae and Haemophilus spp. No breakpoints have been determined for *M. catarrhalis*.
- In EUCAST v. 10.0 (2020), breakpoints for S. pneumoniae with levofloxacin and *H. influenzae* with amoxicillin-clavulanate. isolates that previously were susceptible are now categorized as "susceptibleincreased exposure. intermediate."
- Multidrug-resistant (MDR) S. pneumoniae isolates were categorized as being nonsusceptible (NS) to amoxicillin-clavulanate, erythromycin (ERY), and tetracycline using EUCAST criteria.
- The nitrocefin test (Cefinase, BBL) was used to determine the presence of β -lactamase (BL) for Haemophilus species and M. catarrhalis.

Results

- The delafloxacin MIC distributions of the 4 main species, *H. influenzae*, H. parainfluenzae, M. catarrhalis and S. pneumoniae, are shown in Figure 1.
- S. pneumoniae (n=2,835) was the organism most frequently isolated from CA-RTI, followed by *H. influenzae* (n=1,484).
- *M. catarrhalis had 959 isolates, H. parainfluenzae had only 20 isolates.* • Delafloxacin was the most active agent against S. pneumoniae; it had
- the lowest MIC_{50/90} values of 0.015/0.03 mg/L (Table 1). Delafloxacin activities were similar when tested against S. pneumoniae isolates with resistant phenotypes.
- MDR isolates had delafloxacin MIC_{50/90} values of 0.015/0.03 mg/L. • The percent susceptibility of all S. pneumoniae and MDR isolates for
- delafloxacin and comparators are shown in Table 1.
- Delafloxacin susceptibility, based on FDA susceptible breakpoints for S. pneumoniae (<0.03 mg/L), was 95.0%. No EUCAST breakpoints for delafloxacin are available for S. pneumoniae or Haemophilus spp.
- The drugs with the lowest percent susceptibility for S. pneumoniae, using EUCAST breakpoints, were penicillin with 71.8% and erythromycin with 76.8%.
- Using EUCAST criteria, 253 isolates were MDR, which is 8.9% of all isolates.

- Figure 2.
- (Table 2).

- Table 2
- 97.0%.

Table 1 Antimicrobial activity of delafloxacin and comparator agents tested against S. pneumoniae

ntimicrobial a organism/orga group Streptococcus Delafloxacin Levofloxacin Moxifloxacin Amoxicillin-cla

Ceftaroline Ceftriaxone

Clindamycin ythromycin eropener

Penicillin

tracycline imethoprin ulfamethoxaz Multi-drug res Delafloxacin evofloxacin **Aoxifloxacin** noxicillin-cl Ceftaroline Ceftriaxone

Clindamycin Erythromycin eropenem

Penicillin

Fetracycline Frimethoprin ulfamethoxaz

- ^o Using FDA CABP breakpoints. ^c FDA breakpoints published 2019-0CT-29.
- ^e Using non-meningitis breakpoints. ^f Using oral breakpoints.
- ³ Using meningitis breakpoints. ^h Using parenteral, meningitis breakpoints.

The percentage of MDR S. pneumoniae isolates by country is shown in

The country with the largest number of MDR S. pneumoniae was Turkey (n=55, 29.7%).

Delafloxacin was the most active fluoroquinolone against *H. influenzae*

– 18.1% of *H. influenzae*, 5.0% of *H. parainfluenzae*, and 86.9% of *M. catarrhalis* were β -lactamase positive. β -lactamase presence did not affect fluoroquinolone MIC values.

The percent susceptibility of *H. influenzae* and comparators is shown in

Delafloxacin susceptibility against *H. influenzae* (≤0.004 mg/L) was

- For *H. influenzae*, only 61.1% were susceptible to trimethoprimsulfamethoxazole, and the ampicillin resistance was 24.7%. - For the β-lactamase negative *H. influenzae*, 8.1% were ampicillin-R using EUCAST breakpoints (data not shown).

Figure 1 Delafloxacin MIC distribution for respiratory tract pathogens



gent/ ism	No. of isolates		៣រួ	g/L		CLSI ^a		EUCAST ^a			
		MIC ₅₀	MIC ₉₀	MIC range	% S	%	% R	% S	%	% R	
neumoi	niae						1				
	2,835	0.015	0.03	≤0.004 to >4	95.0 b,c						
	2,835	1	2	0.25 to >4	97.9	0.4	1.7	d	97.9	2.1	
	2,715	≤0.12	0.25	≤0.12 to >4	98.5	0.7	0.8	98.5		1.5	
lanic	2,834	≤1	2	≤1 to >4	93.7 ^e	2.6	3.7	83.2 ^f	4.1	12.7	
	2,833	≤0.015	0.12	≤0.015 to >1	99.9			99.8		0.2	
	2,834	≤0.06	1	≤0.06 to >2	86.9 ^g	9.4	3.7	86.9	12.4	0.7	
					96.3 ^e	3.0	0.7				
	2,835	≤0.25	>1	≤0.25 to >1	83.4	0.4	16.2	83.8		16.2	
	2,833	≤0.12	>2	≤0.12 to >2	76.8	0.2	23	76.8	0.2	23	
	2,715	≤0.015	0.5	≤0.015 to >1	85.7	8.8	5.5	85.7 ^g		14.3	
								100.0 e		0	
	2,835	≤0.06	2	≤0.06 to >4	71.8 ^f	15.2	13	71.8 ^g		28.2	
					71.8 ^h		28.2	71.8 ^e	23	5.1	
					94.9 ⁱ	4.6	0.5				
	2,835	≤0.5	>4	≤0.5 to >4	78.8	0.4	20.8	78.8	0.4	20.8	
е	2,835	≤0.5	>4	≤0.5 to >4	73.4	8.7	17.8	78.8	3.4	17.8	
ant S. J	oneumonia	е									
	253	0.015	0.03	≤0.004 to 1	90.9 b,c						
	253	1	2	0.5 to >4	94.5	1.2	4.3	d	94.5	5.5	
	240	≤0.12	0.25	≤0.12 to >4	96.2	1.2	2.5	96.2		3.8	
lanic	253	2	>4	1 to >4	60.9 ^e	17.8	21.3	0.0 f	23.7	76.3	
	252	0.12	0.25	≤0.008 to 1	99.6			98.4		1.6	
	253	1	2	0.12 to >2	17.4 ^g	51	31.6	17.4	76.7	5.9	
					68.4 ^e	25.7	5.9				
	253	>1	>1	≤0.25 to >1	19.8	0.8	79.4	20.6		79.4	
	253	>2	>2	0.5 to >2	0.0	1.2	98.8	0.0	1.2	98.8	
	240	0.5	1	≤0.008 to >1	10.8	54.2	35	10.8 ^g		89.2	
								100.0 e		0	
	253	2	4	0.5 to >4	0.0 f	16.6	83.4	0.0 g		100	
					0.0 h		100.0	0.0 e	64.4	35.6	
					64.4 ⁱ	30.8	4.7				
	253	>4	>4	2 to >4	0.0	1.2	98.8	0.0	1.2	98.8	
е	253	4	>4	≤0.5 to >4	27.7	16.6	55.7	38.3	5.9	55.7	

^a Criteria as published by CLSI (2020) and EUCAST (2020)

^d An arbitrary susceptible breakpoint of <0.001 mg/L and/or >50 mm has been published by EUCAST indicating that susceptible should not be reported for this organism-agent combination and intermediate should be interpreted as susceptible increased exposure (EUCAST 2020).



Table 2 Antimicrobial activity of delafloxacin and comparator agents tested against *H. influenzae*

Antimicrobial agent/	No. of	mg/L		CLSI ^a			EUCAST ^a			
organism/ organism group	isolates	MIC ₅₀	MIC ₉₀	MIC range	% S	%	% R	% S	%	% R
H. influenzae										
Delafloxacin	1,484	≤0.001	0.002	≤0.001 to >0.25	97.0 ^{b,c}					
Levofloxacin	1,484	≤0.015	0.03	≤0.015 to >2	98.9			97.6		2.4
Ciprofloxacin	1,484	0.015	0.015	≤0.008 to >1	98.8			97.8		2.2
Moxifloxacin	1,400	0.03	0.03	≤0.008 to >1	98.7			98.0		2.0
Amoxicillin-clavulanic acid	1,484	0.5	2	≤0.12 to >8	99.7		0.3	d,e	94.6	5.4
								94.6 ^f		5.4
Ampicillin	1,484	0.5	>8	≤0.12 to >8	75.3	6.4	18.3	75.3		24.7
Azithromycin	1,484	1	1	≤0.12 to >8	99.1			99.1 ^g		
Ceftaroline	1,483	0.008	0.03	≤0.004 to 0.5	100.0			98.3		1.7
Ceftriaxone	1,484	≤0.015	≤0.015	≤0.015 to 0.25	100.0			99.9		0.1
Clarithromycin	1,484	8	16	≤0.12 to >16	89.0	9.7	1.3	100.0 ^g		
Meropenem	1,484	0.06	0.12	≤0.008 to 0.5	100.0			99.5 ^h		0.5
								100.0 ⁱ		0.0
Tetracycline	1,484	0.5	1	0.12 to >8	99.2	0.0	0.8	98.8	0.4	0.8
Trimethoprim- sulfamethoxazole	1,483	0.12	>4	≤0.06 to >4	61.1	5.9	33	61.1	2.8	36.1
H. influenzae- BLP										
Delafloxacin	268	≤0.001	0.002	≤0.001 to 0.03	99.6 ^{b,c}					
Levofloxacin	268	≤0.015	0.03	≤0.015 to 1	100.0			99.3		0.7
Ciprofloxacin	268	0.015	0.015	≤0.008 to 1	100.0			99.3		0.7
Moxifloxacin	254	0.03	0.03	0.008 to 1	100.0			99.6		0.4
Amoxicillin-clavulanic acid	268	1	2	0.25 to 8	99.6		0.4	d,e	94.8	5.2
								94.8 f		5.2
Ampicillin	268	>8	>8	1 to >8	0.4	1.5	98.1	0.4		99.6
Azithromycin	268	0.5	1	≤0.12 to >8	98.5			98.5 ^g		
Ceftaroline	268	0.015	0.03	≤0.004 to 0.5	100.0			95.1		4.9
Ceftriaxone	268	≤0.015	≤0.015	≤0.015 to 0.12	100.0			100.0		0.0
Clarithromycin	268	8	8	0.25 to >16	91.0	7.5	1.5	100.0 ^g		
Meropenem	268	0.06	0.12	≤0.008 to 0.5	100.0			99.6 ^h		0.4
								100.0 ⁱ		0.0
Tetracycline	268	0.5	0.5	0.25 to >8	97.4	0.0	2.6	96.3	1.1	2.6
Trimethoprim-sulfamethoxazole	268	0.12	>4	≤0.06 to >4	57.1	2.6	40.3	57.1	0.7	42.2

^a Criteria as published by CLSI (2020) and EUCAST (2020)

^b Using CABP breakpoints.

^c FDA breakpoints published 2019-0CT-29. ^d Using oral breakpoints.

^e An arbitrary susceptible breakpoint of ≤0.001 mg/L and/or >50 mm has been published by EUCAST indicating that susceptible should not be reported for this organism-agent combination and intermediate should be interpreted as susceptible increased exposure (EUCAST 2020). ^f Using parenteral breakpoints

^g Percentage of wild type based on ECV. EUCAST version 10.0 (2020).

^h Using meningitis breakpoints.

¹ Using non-meningitis breakpoints. ^j FDA breakpoints published 2017-DEC-13

Figure 2 Percent of multi-drug resistance S. pneumoniae by country

Conclusions

- Delafloxacin demonstrated potent *in vitro* antibacterial activity against S. pneumoniae, H. influenzae, H. parainfluenzae, and M. catarrhalis.
- Delafloxacin was active against the MDR S. pneumoniae that were nonsusceptible to the agents commonly used as treatments for CABP: amoxicillin-clavulanate, tetracycline, and erythromycin.
- Resistance to fluoroquinolones was rare for all CA-RTI isolates, with $\geq 94\%$ susceptiblity overall.
- These data support the utility of delafloxacin in the treatment of CABP, including infections caused by antibiotic-resistant strains of S. pneumoniae and H. influenzae.

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Contact

Dee Shortridge, PhD JMI Laboratories 345 Beaver Kreek Centre, Suite A North Liberty, Iowa 52317 Phone: (319) 665-3370 Fax: (319) 665-3371 Email: dee-shortridge@jmilabs.com

