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

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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*.

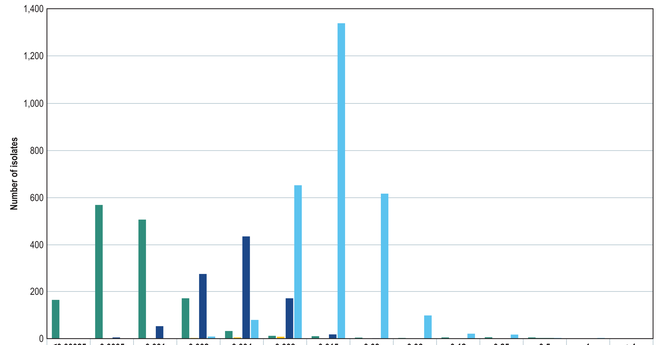
Materials and Methods

- 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 "susceptible-increased 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.
- The percentage of MDR *S. pneumoniae* isolates by country is shown in Figure 2.
  - 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* (Table 2).
  - 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 Table 2.
  - Delafloxacin susceptibility against *H. influenzae* (≤0.004 mg/L) was 97.0%.
  - For *H. influenzae*, only 61.1% were susceptible to trimethoprim-sulfamethoxazole, 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



	≤0.00025	0.0005	0.001	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	>4
Haemophilus influenzae	164	567	505	171	32	12	10	4	3	5	6	5		
Haemophilus parainfluenzae		1		3	5	8		1		1		1		
Moraxella catarrhalis		5	53	274	434	171	18	2	1	1				
Streptococcus pneumoniae				9	79	651	1,338	615	98	21	17	3	3	1

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

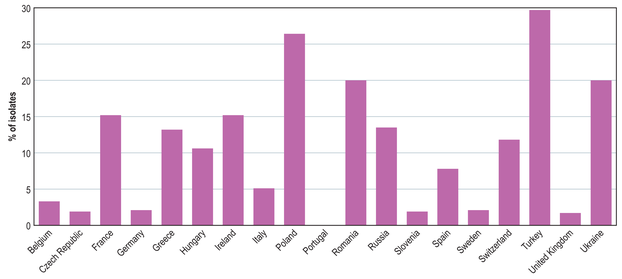


Table 1 Antimicrobial activity of delafloxacin and comparator agents tested against *S. pneumoniae*

Antimicrobial agent/ organism/organism group	No. of isolates	mg/L			CLSI[a]			EUCAST[a]		
		MIC_{50}	MIC_{90}	MIC range	%S	%I	%R	%S	%I	%R
Streptococcus pneumoniae										
Delafloxacin	2,835	0.015	0.03	≤0.004 to >4	95.0 [b,c]					
Levofloxacin	2,835	1	2	0.25 to >4	97.9	0.4	1.7	[d]	97.9	2.1
Moxifloxacin	2,715	≤0.12	0.25	≤0.12 to >4	98.5	0.7	0.8	98.5		1.5
Amoxicillin-clavulanic acid	2,834	≤1	2	≤1 to >4	93.7 [e]	2.6	3.7	83.2 [f]	4.1	12.7
Ceftaroline	2,833	≤0.015	0.12	≤0.015 to >1	99.9			99.8		0.2
Ceftriaxone	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			
Clindamycin	2,835	≤0.25	>1	≤0.25 to >1	83.4	0.4	16.2	83.8		16.2
Erythromycin	2,833	≤0.12	>2	≤0.12 to >2	76.8	0.2	23	76.8	0.2	23
Meropenem	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
Penicillin	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			
Tetracycline	2,835	≤0.5	>4	≤0.5 to >4	78.8	0.4	20.8	78.8	0.4	20.8
Trimethoprim-sulfamethoxazole	2,835	≤0.5	>4	≤0.5 to >4	73.4	8.7	17.8	78.8	3.4	17.8
Multi-drug resistant *S. pneumoniae*										
Delafloxacin	253	0.015	0.03	≤0.004 to 1	90.9 [b,c]					
Levofloxacin	253	1	2	0.5 to >4	94.5	1.2	4.3	[d]	94.5	5.5
Moxifloxacin	240	≤0.12	0.25	≤0.12 to >4	96.2	1.2	2.5	96.2		3.8
Amoxicillin-clavulanic acid	253	2	>4	1 to >4	60.9 [e]	17.8	21.3	0.0 [f]	23.7	76.3
Ceftaroline	252	0.12	0.25	≤0.008 to 1	99.6			98.4		1.6
Ceftriaxone	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			
Clindamycin	253	>1	>1	≤0.25 to >1	19.8	0.8	79.4	20.6		79.4
Erythromycin	253	>2	>2	0.5 to >2	0.0	1.2	98.8	0.0	1.2	98.8
Meropenem	240	0.5	1	≤0.008 to >1	10.8	54.2	35	10.8 [g]		89.2
								100.0 [e]		0
Penicillin	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			
Tetracycline	253	>4	>4	2 to >4	0.0	1.2	98.8	0.0	1.2	98.8
Trimethoprim-sulfamethoxazole	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).
[b] Using FDA CABP breakpoints.
[c] FDA breakpoints published 2019-OCT-29.
[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).
[e] Using non-meningitis breakpoints.
[f] Using oral breakpoints.
[g] Using meningitis breakpoints.
[h] Using parenteral, meningitis breakpoints.
[i] Using parenteral, non-meningitis breakpoints.

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

Antimicrobial agent/ organism/ organism group	No. of isolates	mg/L			CLSI[a]			EUCAST[a]		
		MIC_{50}	MIC_{90}	MIC range	%S	%I	%R	%S	%I	%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-OCT-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.
[i] Using non-meningitis breakpoints.
[j] FDA breakpoints published 2017-DEC-13.

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 non-susceptible 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 ≥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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