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In Vitro Activity of Lefamulin Against Bacterial Pathogens Causing Community-Acquired Bacterial Pneumonia: SENTRY Surveillance 2017–2018 Results From the United States

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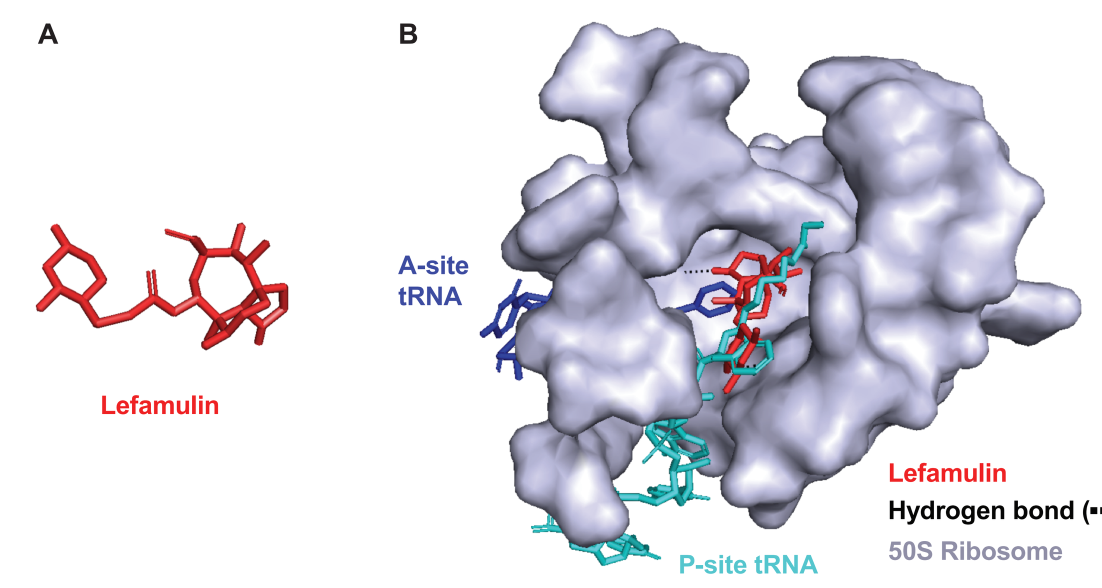
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INTRODUCTION & PURPOSE

- Pneumonia is one of the leading causes of infection-related death in the United States (US)[1] and is associated with substantial morbidity, mortality, and economic burden[2]
- *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Moraxella catarrhalis,* and the atypical pathogens *Mycoplasma pneumoniae, Chlamydophila pneumoniae,* and *Legionella pneumophila,* are among the most common pathogens that cause community-acquired bacterial pneumonia (CABP) and are usually treated with macrolides, β-lactams, or fluoroquinolones[2,3]
 - Surveillance programs have observed trends of generally decreasing antimicrobial susceptibility for *S. pneumoniae* strains in North America, including 64.1% and 56.1% susceptibility to penicillin (using oral breakpoints) and erythromycin, respectively[4]
 - Methicillin-resistant *S. aureus* (MRSA) has emerged as an important CABP-causing pathogen because of its disproportionate frequency of infecting young, otherwise healthy patients[5]; in the US, methicillin-resistance rates range from 40.7%–54.7%, depending on the region[6]
 - Increasing rates of antimicrobial resistance, combined with increasing safety concerns associated with fluoroquinolones,[7,8] have created a need for new safe and effective treatment options[2]
- Lefamulin (LEF) is the first antimicrobial in the pleuromutilin class approved for intravenous (IV) and oral administration in adults with CABP.[9] LEF selectively inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit at the A- and P-sites in the peptidyl transferase center[10,11] **(Figure 1)**
- In patients with CABP, LEF demonstrated noninferiority to moxifloxacin in the IV-to-oral switch Lefamulin Evaluation Against Pneumonia (LEAP) 1 phase 3 study,[12] and in the LEAP 2 oral-only phase 3 study[13]
- The objective of this analysis was to investigate the in vitro activity of LEF and comparators against a contemporary set of CABP-causing pathogens collected in the US in 2017 and 2018

Figure 1. (A) Structure of Lefamulin and (B) Lefamulin in the Peptidyl Transferase Center of the Large Ribosomal Subunit



A
B
Lefamulin
A-site tRNA
P-site tRNA
Lefamulin
Hydrogen bond (••)
50S Ribosome

METHODS

- As part of the SENTRY Antimicrobial Surveillance Program, 2299 unique isolates (1 per patient) were collected from 34 US medical centers in 2017 and 2018 from patients with community-acquired respiratory tract infections (1812/2299 [78.8%]) and hospitalized patients with pneumonia (487/2299 [21.2%])
- Minimum inhibitory concentration (MIC) for LEF and comparators was determined using Clinical and Laboratory Standards Institute (CLSI) broth microdilution[14]; susceptibility was evaluated using the CLSI (2019) breakpoints[15]

RESULTS

- LEF demonstrated potent antibacterial activity against all tested CABP pathogens, and its activity was unaffected by resistance to other antibiotic classes

S. pneumoniae

- *S. pneumoniae* isolates showed considerable resistance to macrolides (45.6%), penicillin (36.8%), and tetracycline (20.4%), whereas they were largely susceptible (>85%) to the tested cephalosporins and fluoroquinolones **(Table 1)**
- LEF was highly active against *S. pneumoniae*, with a minimum concentration at which 50% or 90% of the isolates were inhibited ($MIC_{50/90}$) of 0.12/0.25 µg/mL (range ≤0.008–2 µg/mL; **Table 1**)
- LEF was effective against all tested resistant subsets ($MIC_{50/90}$ of 0.12/0.25 µg/mL), with 100% of penicillin- and tetracycline-resistant isolates and 99.5% of macrolide-resistant isolates inhibited at ≤0.5 µg/mL **(Table 2)**

S. aureus

- *S. aureus* isolates overall, and particularly MRSA and fluoroquinolone-resistant strains, were commonly resistant to macrolides; 81.2% of MRSA and 80.4% of fluoroquinolone-resistant strains were resistant to erythromycin (**Table 3**)
- LEF demonstrated potent activity against *S. aureus* isolates, including methicillin-resistant, macrolide-resistant (75.0% MRSA) and fluoroquinolone-resistant (87.6% MRSA) subsets ($MIC_{50/90}$ of 0.06/0.12 µg/mL for each; **Table 3**)

H. influenzae

- *H. influenzae* isolates were largely susceptible to all comparators except ampicillin (31.4% resistant) and trimethoprim-sulfamethoxazole (35.3% resistant; **Table 4**)
- LEF demonstrated activity against *H. influenzae* ($MIC_{50/90}$ of 0.5/2 µg/mL; **Table 4**), with 99.2% of isolates inhibited at ≤2 µg/mL

M. catarrhalis

- *M. catarrhalis* isolates included a large proportion (97.6%) of β-lactamase producers and were susceptible (96.4%–100%) to all comparators, including amoxicillin-clavulanic acid (**Table 4**)
- LEF inhibited all *M. catarrhalis* isolates at concentrations of ≤0.5 µg/mL ($MIC_{50/90}$ of 0.06/0.12 µg/mL; **Table 4**)

β-hemolytic streptococci

- LEF effectively inhibited β-hemolytic streptococci (*n*=14), with $MIC_{50/90}$ values of 0.03/0.06 µg/mL (data not shown)

Table 1. Activity of Lefamulin and Comparators Against *S. pneumoniae*

Antimicrobial Agent	(µg/mL) MIC50	MIC90	Range	CLSI* %S	%I	%R
***S. pneumoniae* (n=1441)**						
Lefamulin	**0.12**	**0.25**	**≤0.008–2**	**99.8†**	**–**	**–**
Amoxicillin-clavulanic acid‡	≤0.03	2	≤0.03–>4	95.1	1.9	3.0
Azithromycin‡	0.12	>4	≤0.03–>4	53.0	1.4	45.6
Ceftaroline	≤0.008	0.12	≤0.008–0.5	100.0	–	–
Ceftriaxone§	0.03	1	≤0.015–>2	86.0‖	11.0	2.9
				97.1¶	2.5	0.4
Clindamycin	≤0.25	>2	≤0.25–>2	85.2	0.4	14.4
Erythromycin	0.06	>16	≤0.015–>16	53.9	0.6	45.6
Levofloxacin	1	1	0.25–>4	99.2	0.1	0.7
Moxifloxacin	0.12	0.25	≤0.03–4	99.4	0.5	0.1
Penicillin	0.03	2	≤0.008–>4	63.2^	26.0	10.8
				63.2#	–	36.8
				96.3**	3.1	0.7
Tetracycline‡	0.5	>4	0.06–>4	79.6	0.1	20.4
Trimethoprim-sulfamethoxazole	0.25	>4	≤0.12–>4	73.6	11.7	14.8

CLSI=Clinical and Laboratory Standards Institute; I=intermediate; MIC_{50}=minimum concentration at which 50% of isolates were inhibited; MIC_{90}=minimum concentration at which 90% of isolates were inhibited; R=resistant; S=susceptible.
*2019 CLSI criteria. †2019 FDA susceptibility breakpoint of ≤0.5 µg/mL applied. ‡*n*=1439. §*n*=1440. ‖Using meningitis breakpoints. ¶Using nonmeningitis breakpoints. ^Using oral breakpoints. #Using parenteral, meningitis breakpoints. **Using parenteral, nonmeningitis breakpoints.

Table 2. Activity of Lefamulin and Comparators Against Drug-Resistant *S. pneumoniae*

Antimicrobial Agent	(µg/mL) MIC50	MIC90	Range	CLSI* %S	%I	%R
Penicillin-resistant† *S. pneumoniae* (n=156)						
Lefamulin	**0.12**	**0.25**	**0.015–0.25**	**100.0‡**	**–**	**–**
Amoxicillin-clavulanic acid	2	>4	1–>4	55.1	17.3	27.6
Azithromycin	>4	>4	0.06–>4	5.8	0.0	94.2
Ceftaroline	0.12	0.25	0.06–0.5	100.0	–	–
Ceftriaxone	1	2	0.5–>2	5.8§	67.9	26.3
				73.7‖	22.4	3.8
Clindamycin	≤0.25	>2	≤0.25–>2	57.7	0.6	41.7
Erythromycin	16	>16	0.03–>16	5.8	0.0	94.2
Levofloxacin	1	1	0.5–>4	98.7	0.0	1.3
Moxifloxacin	0.12	0.25	0.06–2	99.4	0.6	0.0
Penicillin	2	4	2–>4	0.0¶	0.0	100.0
				0.0^	–	100.0
				65.4#	28.2	6.4
Tetracycline	1	>4	0.12–>4	50.0	0.0	50.0
Trimethoprim-sulfamethoxazole	>4	>4	≤0.12–>4	26.3	5.1	68.6
Macrolide-resistant *S. pneumoniae* (n=657)**						
Lefamulin	**0.12**	**0.25**	**0.015–2**	**99.5‡**	**–**	**–**
Amoxicillin-clavulanic acid	0.25	4	≤0.03–>4	89.5	4.0	6.5
Azithromycin	>4	>4	0.06–>4	0.2	1.4	98.5
Ceftaroline	0.06	0.12	≤0.008–0.5	100.0	–	–
Ceftriaxone	0.25	1	≤0.015–>2	71.5§	22.1	6.4
				93.6‖	5.5	0.9
Clindamycin	≤0.25	>2	≤0.25–>2	67.9	0.8	31.4
Erythromycin	8	>16	1–>16	0.0	0.0	100.0
Levofloxacin	1	1	0.5–>4	99.2	0.2	0.6
Moxifloxacin	0.12	0.25	≤0.03–2	99.5	0.5	0.0
Penicillin	0.25	2	≤0.008–>4	33.0¶	44.6	22.4
				33.0^	–	67.0
				91.8#	6.7	1.5
Tetracycline	0.5	>4	0.06–>4	60.0	0.0	40.0
Trimethoprim-sulfamethoxazole	0.5	>4	≤0.12–>4	53.9	18.9	27.2
Tetracycline-resistant *S. pneumoniae* (n=293)						
Lefamulin	**0.12**	**0.25**	**0.015–0.5**	**100.0‡**	**–**	**–**
Amoxicillin-clavulanic acid	0.25	>4	≤0.03–>4	79.9	6.5	13.7
Azithromycin††	>4	>4	≤0.03–>4	6.8	2.1	91.1
Ceftaroline	0.06	0.12	≤0.008–0.5	100.0	–	–
Ceftriaxone	0.25	2	≤0.015–>2	71.3§	15.7	13.0
				87.0‖	11.6	1.4
Clindamycin	>2	>2	≤0.25–>2	33.1	1.4	65.5
Erythromycin	>16	>16	≤0.015–>16	9.2	1.0	89.8
Levofloxacin	1	2	0.5–>4	99.0	0.3	0.7
Moxifloxacin	0.12	0.25	0.06–2	99.7	0.3	0.0
Penicillin	0.25	4	≤0.008–>4	21.2¶	52.2	26.6
				21.2^	–	78.8
				83.6#	13.3	3.1
Tetracycline	>4	>4	4–>4	0.0	0.0	100.0
Trimethoprim-sulfamethoxazole	1	>4	≤0.12–>4	39.6	24.9	35.5

CLSI=Clinical and Laboratory Standards Institute; I=intermediate; MIC=minimum inhibitory concentration; MIC_{50}=minimum concentration at which 50% of isolates were inhibited; MIC_{90}=minimum concentration at which 90% of isolates were inhibited; R=resistant; S=susceptible.
*2019 CLSI criteria. †Penicillin MIC ≥2 µg/mL for oral breakpoint. ‡2019 FDA susceptibility breakpoint of ≤0.5 µg/mL applied. §Using meningitis breakpoints. ‖Using nonmeningitis breakpoints. ¶Using oral breakpoints. ^Using parenteral, meningitis breakpoints. #Using parenteral, nonmeningitis breakpoints. **Using erythromycin breakpoints. ††*n*=292.

Table 3. Activity of Lefamulin and Comparators Against *S. aureus*

Antimicrobial Agent	(µg/mL) MIC50	MIC90	Range	CLSI* %S	%I	%R
***S. aureus* (n=297)**						
Lefamulin	**0.06**	**0.12**	**0.03–0.25**	**100.0†**	**–**	**–**
Azithromycin	32	>32	0.12–>32	46.5	0.3	53.2
Ceftaroline	0.25	1	≤0.06–2	94.3‡	5.7	0.0
Clindamycin	0.06	>2	≤0.03–>2	79.5	0.0	20.5
Doxycycline	0.12	0.5	≤0.06–>8	98.0	1.7	0.3
Erythromycin	4	>8	≤0.06–>8	46.5	5.1	48.5
Gentamicin	≤1	≤1	≤1–>8	96.6	0.3	3.0
Levofloxacin	0.25	>4	0.12–>4	62.0	0.0	38.0
Linezolid	1	2	0.25–4	100.0	–	0.0
Moxifloxacin	≤0.06	>4	≤0.06–>4	62.0	5.4	32.7
Oxacillin	1	>2	0.12–>2	55.2	–	44.8
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–>16	98.7	–	1.3
Vancomycin	1	1	0.25–2	100.0	0.0	0.0
MRSA (n=133)						
Lefamulin	**0.06**	**0.12**	**0.03–0.25**	**100.0†**	**–**	**–**
Azithromycin	>32	>32	0.12–>32	14.3	0.0	85.7
Ceftaroline	1	2	0.25–2	87.2‡	12.8	0.0
Clindamycin	0.06	>2	≤0.03–>2	58.6	0.0	41.4
Doxycycline	0.12	1	≤0.06–8	97.0	3.0	0.0
Erythromycin	>8	>8	≤0.06–>8	14.3	4.5	81.2
Gentamicin	≤1	≤1	≤1–>8	94.7	0.0	5.3
Levofloxacin	>4	>4	0.12–>4	26.3	0.0	73.7
Linezolid	1	2	0.25–2	100.0	–	0.0
Moxifloxacin	2	>4	≤0.06–>4	26.3	9.8	63.9
Oxacillin	>2	>2	>2–>2	0.0	–	100.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–>16	97.0	–	3.0
Vancomycin	1	1	0.5–2	100.0	0.0	0.0
Macrolide-resistant§ *S. aureus* (n=144)						
Lefamulin	**0.06**	**0.12**	**0.03–0.25**	**100.0†**	**–**	**–**
Azithromycin	>32	>32	8–>32	0.0	0.0	100.0
Ceftaroline	0.5	2	≤0.06–2	88.2‡	11.8	0.0
Clindamycin	0.06	>2	≤0.03–>2	57.6	0.0	42.4
Doxycycline	0.12	1	≤0.06–>8	96.5	2.8	0.7
Erythromycin	>8	>8	8–>8	0.0	0.0	100.0
Gentamicin	≤1	≤1	≤1–>8	94.4	0.0	5.6
Levofloxacin	>4	>4	0.12–>4	35.4	0.0	64.6
Linezolid	1	2	0.25–2	100.0	–	0.0
Moxifloxacin	2	>4	≤0.06–>4	35.4	10.4	54.2
Oxacillin	>2	>2	0.25–>2	25.0	–	75.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–>16	98.6	–	1.4
Vancomycin	1	1	0.5–2	100.0	0.0	0.0
Fluoroquinolone-resistant‖ *S. aureus* (n=97)						
Lefamulin	**0.06**	**0.12**	**0.03–0.25**	**100.0†**	**–**	**–**
Azithromycin	>32	>32	0.25–>32	14.4	1.0	84.5
Ceftaroline	1	2	0.12–2	82.5‡	17.5	0.0
Clindamycin	>2	>2	≤0.03–>2	47.4	0.0	52.6
Doxycycline	0.12	1	≤0.06–8	96.9	3.1	0.0
Erythromycin	>8	>8	≤0.06–>8	14.4	5.2	80.4
Gentamicin	≤1	≤1	≤1–>8	92.8	0.0	7.2
Levofloxacin	>4	>4	4–>4	0.0	0.0	100.0
Linezolid	1	2	0.5–2	100.0	–	0.0
Moxifloxacin	>4	>4	2–>4	0.0	0.0	100.0
Oxacillin	>2	>2	0.25–>2	12.4	–	87.6
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–>16	95.9	–	4.1
Vancomycin	1	1	0.5–2	100.0	0.0	0.0

CLSI=Clinical and Laboratory Standards Institute; I=intermediate; MIC_{50}=minimum concentration at which 50% of isolates were inhibited; MIC_{90}=minimum concentration at which 90% of isolates were inhibited; MRSA=methicillin-resistant *S. aureus*; MSSA=methicillin-susceptible *S. aureus*; R=resistant; S=susceptible.
*2019 CLSI criteria. †2019 FDA susceptibility breakpoint for MSSA of ≤0.25 µg/mL applied. ‡Intermediate interpreted as susceptible-dose dependent. §Using erythromycin breakpoints. ‖Using moxifloxacin breakpoints.

Table 4. Activity of Lefamulin and Comparators Against *H. influenzae* and *M. catarrhalis*

Antimicrobial Agent	(µg/mL) MIC50	MIC90	Range	CLSI* %S	%I	%R
***H. influenzae* (n=382)**						
Lefamulin	**0.5**	**2**	**0.015–8**	**99.2†**	**–**	**–**
Amoxicillin-clavulanic acid	0.5	2	≤0.06–>8	99.2	–	0.8
Ampicillin	0.5	>8	≤0.12–>8	65.4	3.1	31.4
Azithromycin	1	2	≤0.12–>8	98.4	–	–
Cefepime	0.12	0.25	≤0.015–>2	99.7	–	–
Ceftriaxone	0.004	0.015	≤0.002–0.25	100.0	–	–
Ciprofloxacin	0.015	0.015	0.008–>1	98.7	–	–
Clarithromycin	8	16	≤0.12–>16	80.9	16.2	2.9
Moxifloxacin	0.03	0.06	0.015–>2	99.0	–	–
Tetracycline	0.5	1	0.12–>8	99.0	0.0	1.0
Trimethoprim-sulfamethoxazole	0.12	>4	≤0.06–>4	62.0	2.6	35.3
***M. catarrhalis* (n=165)**						
Lefamulin	**0.06**	**0.12**	**≤0.008–0.12**	**–**	**–**	**–**
Amoxicillin-clavulanic acid	≤0.25	≤0.25	≤0.25–0.5	100.0	–	0.0
Azithromycin	≤0.03	≤0.03	≤0.03–0.06	100.0	–	–
Ceftriaxone	0.25	1	0.004–2	100.0	–	–
Clarithromycin	≤0.12	≤0.12	≤0.12–0.5	100.0	–	–
Moxifloxacin	0.06	0.06	0.015–0.12	–	–	–
Tetracycline	0.25	0.5	0.12–>8	99.4	0.0	0.6
Trimethoprim-sulfamethoxazole	0.12	0.25	≤0.06–2	96.4	3.6	0.0

CLSI=Clinical and Laboratory Standards Institute; I=intermediate; MIC_{50}=minimum concentration at which 50% of isolates were inhibited; MIC_{90}=minimum concentration at which 90% of isolates were inhibited; R=resistant; S=susceptible.
*2019 CLSI criteria. †2019 FDA susceptibility breakpoint of ≤2 µg/mL applied.

CONCLUSIONS

- LEF demonstrated potent in vitro activity against this contemporary (2017–2018) set of pathogens collected in the US from patients with respiratory tract infections and hospitalized patients with pneumonia
- LEF activity was comparable with the most common antimicrobial agents used to treat CABP and was unaffected by resistance to other antibiotic classes, including macrolides, fluoroquinolones, β-lactams, and tetracyclines
- These in vitro data, as well as the high efficacy in CABP patients from phase 3 clinical trials (LEAP 1 and 2),[12,13] suggest that LEF may offer an important empiric monotherapy treatment option for CABP, particularly where resistance to antimicrobial agents commonly used to treat CABP is high

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