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Lefamulin Activity Against Gram-Positive Pathogens Collected in the 2017 Global SENTRY Antimicrobial Surveillance Program

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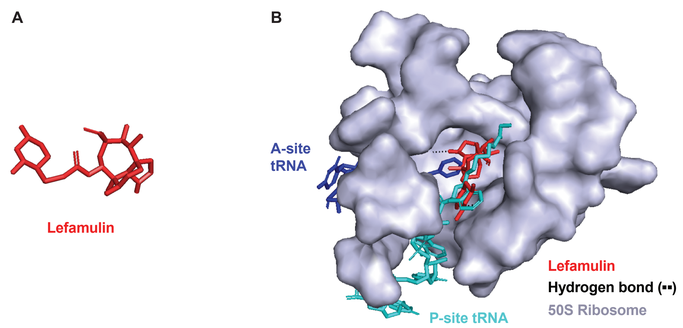
INTRODUCTION & PURPOSE

- Pneumonia is a major cause of morbidity and mortality in adults and children around the world.[1-5] Although antibiotic resistance rates vary by geographic region, rates are rising worldwide, creating a need for new therapies to treat community-acquired bacterial pneumonia (CABP)[3-5]
- *Streptococcus pneumoniae* is the most commonly isolated bacterial pathogen from patients with CABP, with prevalences that vary by geographic region. Other causes of CABP include *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*, as well as atypical pathogens[2,5]
- Lefamulin (LEF), the first pleuromutilin antibiotic to be approved for intravenous (IV) and oral treatment of adults with CABP,[6] selectively inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit at the A- and P-sites in the peptidyl transferase center[7,8] **(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[9] and in the LEAP 2 oral-only phase 3 study[10]
- The objective of this study was to evaluate the in vitro activity of LEF and comparators against a contemporary global set of gram-positive pathogens

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



METHODS

- As part of the 2017 global SENTRY Antimicrobial Surveillance Program, 4337 unique isolates (1 per patient) were collected from patients with community-acquired respiratory tract infections (40.0%), hospitalized patients with pneumonia (13.6%), bloodstream infections (23.2%), skin and soft tissue infections (18.7%), and other infections (4.5%)
- Isolates were collected from 98 sites in 34 countries
  - 36.8% of isolates were collected from the United States, 38.8% from Europe, 13.1% from the Asia-Pacific region, and 11.3% from Latin America
- Minimum inhibitory concentration (MIC) for LEF and comparators was determined using Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods[11]; susceptibility was evaluated using the CLSI (2019) breakpoints[12]

RESULTS

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

Streptococcus pneumoniae

- *S. pneumoniae* isolates were largely susceptible to moxifloxacin (98.0%–100%) and amoxicillin-clavulanic acid (88.5%–94.8%; **Table 1**)
- In contrast, only 38.2%–76.2% and 44.5%–71.9% were susceptible to azithromycin and oral penicillin, respectively, with the lowest susceptibility rates observed in the Asia-Pacific region **(Table 1)**
- LEF inhibited all *S. pneumoniae* isolates at ≤1 µg/mL, and the concentrations at which 50% and 90% of isolates were inhibited ($MIC_{50/90}$) were 0.12/0.25 µg/mL **(Table 1)**

β-hemolytic streptococci

- β-hemolytic streptococcal isolates were largely susceptible to all antimicrobial agents; the lowest susceptibility rates were to erythromycin in the United States (65.5%; **Table 2**)
- LEF inhibited 99.5% of β-hemolytic streptococcal isolates at ≤0.12 µg/mL, with $MIC_{50/90}$ values of 0.03/0.03 µg/mL **(Table 2)**

Staphylococcus aureus

- Overall, *S. aureus* isolates had reduced susceptibility rates to macrolides (42.6%–76.1%, erythromycin) and fluoroquinolones (62.9%–83.8%, levofloxacin; **Table 3**)
- Similarly, only 12.9%–43.2% and 30.7%–45.6% of methicillin-resistant *S. aureus* (MRSA) strains were susceptible to erythromycin and levofloxacin, respectively, with the lowest susceptibility rates for erythromycin observed in the United States and for levofloxacin observed in the United States and Europe **(Table 3)**
- LEF displayed potent activity against *S. aureus* as well as the MRSA subset, with $MIC_{50/90}$ values of 0.06/0.12 µg/mL for both **(Table 3)**

Coagulase-negative staphylococci

- Coagulase-negative staphylococci showed particularly reduced susceptibility rates to azithromycin (23.6%–45.8%), erythromycin (23.6%–45.8%), and oxacillin (20.8%–39.8%; **Table 4**)
- LEF also showed potent activity against coagulase-negative staphylococci ($MIC_{50/90}$ of 0.06/0.5 µg/mL; **Table 4**)

RESULTS (continued)

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

Antimicrobial Agent	$MIC_{50/90}$ (µg/mL)	% Susceptible per CLSI (M100, 2019)			
		USA	Europe	Latin America	Asia-Pacific
S. pneumoniae	***n*=2095**	***n*=832**	***n*=950**	***n*=113**	***n*=200**
Lefamulin	**0.12/0.25**	**[100.0]***	**[100.0]***	**[100.0]***	**[100.0]***
Amoxicillin-clavulanic acid	≤0.03/2	94.8	93.2	88.5	90.9
Azithromycin	0.06/>4	55.4	76.2	67.0	38.2
Ceftaroline	≤0.008/0.12	100.0	99.9	99.1	100.0
Ceftriaxone	0.03/1	85.8†	86.5†	81.4†	69.3†
		96.6‡	96.1‡	92.0‡	84.9‡
Clindamycin	≤0.25/>2	85.4	81.9	81.4	56.0
Erythromycin	0.03/>16	55.4	76.3	67.3	38.0
Levofloxacin	1/2	98.9	97.5	100.0	97.0
Moxifloxacin	0.12/0.25	99.2	98.1	100.0	98.0
Penicillin	0.03/2	63.9§	71.9§	62.8§	44.5§
		63.9‖	71.9‖	62.8‖	44.5‖
		95.8¶	94.5¶	88.5¶	89.0¶
Tetracycline	0.5/>4	79.9	77.4	70.8	40.0
Tigecycline	0.06/0.06	94.6^	94.0^	94.7^	89.5^
Trimethoprim-sulfamethoxazole	0.25/>4	73.6	73.8	60.2	59.0

% Susceptibility
■ ≤30.0% ■ 30.1%–50.0% ■ 50.1%–60.0% ■ 60.1%–70.0% ■ 70.1%–85.0% ■ >85.0%
CLSI=Clinical and Laboratory Standards Institute; $MIC_{50/90}$=minimum concentration at which 50% and 90% of isolates were inhibited. *Percentage inhibited at proposed lefamulin breakpoint of ≤1 µg/mL for *S. pneumoniae* is shown in brackets for comparison purposes only. †Using meningitis breakpoints. ‡Using nonmeningitis breakpoints. §Using oral breakpoints. ‖Using parenteral, meningitis breakpoints. ¶Using parenteral, nonmeningitis breakpoints. ^US Food and Drug Administration breakpoints accessed February 2018.

Table 2. Activity of Lefamulin and Comparators Against β-Hemolytic *Streptococcus* spp.

Antimicrobial Agent	$MIC_{50/90}$ (µg/mL)	% Susceptible per CLSI (M100, 2019)			
		USA*	Europe*	Latin America†	Asia-Pacific†
β-hemolytic *Streptococcus* spp.	***n*=430**	***n*=145**	***n*=145**	***n*=70**	***n*=70**
Lefamulin	**0.03/0.03**	**[100.0]‡**	**[100.0]‡**	**[100.0]‡**	**[97.1]‡**
Ceftriaxone	0.03/0.06	100.0	100.0	100.0	100.0
Clindamycin	≤0.25/>2	82.8	83.4	91.4	82.9
Daptomycin	≤0.06/0.25	100.0	100.0	100.0	100.0
Erythromycin	0.03/>16	65.5	77.9	78.6	80.0
Levofloxacin	1/1	100.0	99.3	88.6	97.1
Linezolid	1/2	100.0	100.0	100.0	100.0
Meropenem	0.015/0.06	100.0	100.0	100.0	100.0
Moxifloxacin	0.12/0.25	–	–	–	–
Penicillin	0.015/0.06	100.0	100.0	100.0	100.0
Tigecycline	0.06/0.06	100.0§	100.0§	100.0§	100.0§
Trimethoprim-sulfamethoxazole	≤0.12/0.25	–	–	–	–
Vancomycin	0.5/0.5	100.0	100.0	100.0	100.0

% Susceptibility
■ ≤30.0% ■ 30.1%–50.0% ■ 50.1%–60.0% ■ 60.1%–70.0% ■ 70.1%–85.0% ■ >85.0%
CLSI=Clinical and Laboratory Standards Institute; $MIC_{50/90}$=minimum concentration at which 50% and 90% of isolates were inhibited. *Organisms included: *Streptococcus agalactiae* (*n*=60), *S. dysgalactiae* (*n*=25), and *S. pyogenes* (*n*=60). †Organisms included: *S. agalactiae* (*n*=30), *S. dysgalactiae* (*n*=10), and *S. pyogenes* (*n*=30). ‡Percentage inhibited at proposed lefamulin breakpoint of ≤0.25 µg/mL for β-hemolytic *Streptococcus spp.* is shown in brackets for comparison purposes only. §US Food and Drug Administration breakpoints accessed February 2018.

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

Antimicrobial Agent	$MIC_{50/90}$ (µg/mL)	% Susceptible per CLSI (M100, 2019)			
		USA	Europe	Latin America	Asia-Pacific
S. aureus	***n*=1544**	***n*=537**	***n*=506**	***n*=251**	***n*=250**
Lefamulin	**0.06/0.12**	**[99.4]***	**[99.4]***	**[99.2]***	**[100.0]***
Azithromycin	0.5/>32	43.2	76.5	55.0	65.2
Ceftaroline	0.25/1	97.0†	97.2†	94.4†	89.6†
Clindamycin	0.06/>2	83.2	96.2	85.3	82.8
Doxycycline	0.12/0.5	98.1	99.0	99.6	88.8
Erythromycin	0.25/>8	42.6	76.1	55.0	64.8
Gentamicin	≤1/≤1	97.0	95.5	90.0	82.4
Levofloxacin	0.25/>4	62.9	83.8	82.1	75.6
Linezolid	1/2	100.0	100.0	100.0	100.0
Moxifloxacin	≤0.06/4	63.1	84.0	82.9	75.6
Oxacillin	0.5/>2	55.1	82.6	74.9	58.8
Tigecycline	0.06/0.12	100.0‡	100.0‡	100.0‡	100.0‡
Trimethoprim-sulfamethoxazole	≤0.5/≤0.5	97.8	99.4	99.6	95.6
Vancomycin	1/1	100.0	100.0	100.0	100.0
MRSA	***n*=495**	***n*=241**	***n*=88**	***n*=63**	***n*=103**
Lefamulin	**0.06/0.12**	**[98.8]***	**[96.6]***	**[98.4]***	**[100.0]***
Azithromycin	>32/>32	13.3	43.2	27.0	39.8
Ceftaroline	0.5/2	93.4†	84.1†	77.4†	74.8†
Clindamycin	0.06/>2	70.1	79.5	52.4	61.2
Doxycycline	0.12/2	97.5	96.6	98.4	73.8
Erythromycin	>8/>8	12.9	43.2	27.0	38.8
Gentamicin	≤1/>8	95.4	85.2	76.2	67.0
Levofloxacin	>4/>4	30.7	30.7	38.1	45.6
Linezolid	1/2	100.0	100.0	100.0	100.0
Moxifloxacin	2/>4	31.1	30.7	39.7	45.6
Oxacillin	>2/>2	0.0	0.0	0.0	0.0
Tigecycline	0.06/0.25	100.0‡	100.0‡	100.0‡	100.0‡
Trimethoprim-sulfamethoxazole	≤0.5/≤0.5	95.4	98.9	98.4	91.3
Vancomycin	1/1	100.0	100.0	100.0	100.0

% Susceptibility
■ ≤30.0% ■ 30.1%–50.0% ■ 50.1%–60.0% ■ 60.1%–70.0% ■ 70.1%–85.0% ■ >85.0%
CLSI=Clinical and Laboratory Standards Institute; $MIC_{50/90}$=minimum concentration at which 50% and 90% of isolates were inhibited; MRSA=methicillin-resistant *S. aureus*.
*Percentage inhibited at proposed lefamulin breakpoint of ≤0.5 µg/mL for *S. aureus* is shown in brackets for comparison purposes only. †Intermediate interpreted as susceptible-dose dependent. ‡US Food and Drug Administration breakpoints accessed February 2018.

Table 4. Activity of Lefamulin and Comparators Against Coagulase-Negative *Staphylococcus* spp.

Antimicrobial Agent	$MIC_{50/90}$ (µg/mL)	% Susceptible per CLSI (M100, 2019)			
		USA*	Europe†	Latin America‡	Asia-Pacific§
Coagulase-Negative *Staphylococcus* spp.	***n*=268**	***n*=83**	***n*=82**	***n*=55**	***n*=48**
Lefamulin	**0.06/0.5**	**[92.8]‖**	**[96.3]‖**	**[94.5]‖**	**[91.7]‖**
Azithromycin	32/>32	34.1	45.1	23.6	45.8
Ceftaroline	0.25/1	–	–	–	–
Clindamycin	0.06/>2	66.3	81.7	61.8	72.9
Daptomycin	0.25/0.5	100.0	100.0	100.0	100.0
Doxycycline	0.25/4	88.0	92.7	96.4	91.7
Erythromycin	>8/>8	32.5	45.1	23.6	45.8
Gentamicin	≤1/>8	73.5	56.1	63.6	47.9
Levofloxacin	0.5/>4	63.9	39.0	54.5	60.4
Linezolid	1/1	97.6	98.8	100.0	100.0
Moxifloxacin	0.12/4	65.1	45.1	60.0	64.6
Oxacillin	>2/>2	39.8	30.5	21.8	20.8
Teicoplanin	2/8	97.6	98.8	100.0	91.7
Tigecycline	0.12/0.25	–	–	–	–
Trimethoprim-sulfamethoxazole	≤0.5/16	71.1	58.5	54.5	54.2
Vancomycin	2/2	100.0	100.0	100.0	100.0

% Susceptibility
■ ≤30.0% ■ 30.1%–50.0% ■ 50.1%–60.0% ■ 60.1%–70.0% ■ 70.1%–85.0% ■ >85.0%
CLSI=Clinical and Laboratory Standards Institute; $MIC_{50/90}$=minimum concentration at which 50% and 90% of isolates were inhibited. *Organisms included: *Staphylococcus capitis* (*n*=5), *S. cohnii* (*n*=2), *S. epidermidis* (*n*=45), *S. haemolyticus* (*n*=5), *S. hominis* (*n*=8), *S. lugdunensis* (*n*=9), *S. pettenkoferi* (*n*=1), *S. saprophyticus* (*n*=5), and *S. simulans* (*n*=3). †Organisms included: *S. capitis* (*n*=6), *S. cohnii* (*n*=1), *S. epidermidis* (*n*=42), *S. haemolyticus* (n=17), *S. hominis* (*n*=6), *S. lugdunensis* (*n*=9), and *S. pseudintermedius* (*n*=1). ‡Organisms included: *S. capitis* (*n*=4), *S. cohnii* (*n*=2), *S. epidermidis* (*n*=35), *S. haemolyticus* (*n*=6), *S. hominis* (*n*=5), *S. saprophyticus* (*n*=2), and *S. warneri* (*n*=1). §Organisms included: *S. capitis* (*n*=7), *S. epidermidis* (*n*=21), *S. haemolyticus* (*n*=8), *S. hominis* (*n*=7), *S. lugdunensis* (*n*=3), and *S. warneri* (*n*=2). ‖Percentage inhibited at proposed lefamulin breakpoint of ≤0.5 µg/mL for coagulase-negative *Staphylococcus spp.* is shown in brackets for comparison purposes only.

CONCLUSIONS

- LEF demonstrated potent activity against this contemporary (2017) worldwide collection of gram-positive pathogens
- LEF activity was unaffected by resistance to other antibiotic classes, including macrolides, fluoroquinolones, and β-lactam antibiotics, or by geographic region
- These in vitro data suggest that LEF may offer an important empiric monotherapy treatment option for CABP caused by these organisms, particularly in regions with high rates of resistance to antimicrobials commonly used for CABP

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