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SUSCEPTIBILITY

Antibacterial Activity of Lefamulin against Pathogens Most Commonly Causing Community-Acquired Bacterial Pneumonia: SENTRY Antimicrobial Surveillance Program (2015–2016)

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ABSTRACT Lefamulin, the first semisynthetic pleuromutilin antibacterial for intravenous and oral treatment of community-acquired bacterial pneumonia (CABP), and comparators were evaluated for *in vitro* activity against a global collection of pathogens commonly causing CABP ($n = 8595$) from the 2015 and 2016 SENTRY Antimicrobial Surveillance Program. Lefamulin was highly active against the pathogens *Streptococcus pneumoniae*, including multidrug-resistant and extensively drug-resistant strains ($MIC_{50/90}$ for total and resistant subsets, 0.06/0.12 μg/ml; 100% inhibited at ≤1 μg/ml), *Staphylococcus aureus*, including methicillin-resistant *Staphylococcus aureus* (MRSA; both $MIC_{50/90}$, 0.06/0.12 μg/ml; 99.8% and 99.6% inhibited at ≤1 μg/ml, respectively), *Haemophilus influenzae* ($MIC_{50/90}$, 0.5/1 μg/ml; 93.8% inhibited at ≤1 μg/ml), and *Moraxella catarrhalis* ($MIC_{50/90}$, 0.06/0.12 μg/ml; 100% inhibited at ≤0.25 μg/ml), and its activity was unaffected by resistance to other antibacterial classes.

KEYWORDS antimicrobial, community-acquired bacterial pneumonia, lefamulin, pleuromutilin

Community-acquired bacterial pneumonia (CABP) is a potentially serious respiratory infection with incidence rates of approximately 10.6 cases per 1,000 person-years in the United States (1) and ranges from 1.7 to 11.6 cases per 1,000 person-years as reported from Europe (2). It is a leading cause of hospitalization worldwide (3, 4) and, despite antibiotic treatment, is still a relevant cause of death (4, 5). Together with influenza, community-acquired pneumonia is the eighth most common cause of death in the United States (6). *Streptococcus pneumoniae* is the most commonly isolated pathogen associated with CABP; other common etiologic bacterial pathogens include *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, and the atypical pathogens *Chlamydophila pneumoniae*, *Legionella pneumophila*, and *Mycoplasma pneumoniae* (7, 8). Current recommendations for the treatment of CABP include initiation of empirical antibiotic therapies, which vary depending on the treatment setting, and may include monotherapy with a macrolide, doxycycline, respiratory fluoroquinolone, or combination therapy with a β-lactam plus a macrolide or a respiratory fluoroquinolone (9, 10). As a result of the increasing prevalence of resistance to currently available antimicrobials, particularly penicillin and macrolide resistance among *S. pneumoniae* and macrolide resistance among *M. pneumoniae* (11), high treatment failure rates (14% general hospital ward, ~25% outpatient) (12, 13), and adverse effects associated with current treatment options (14, 15), new treatment options for CABP are needed, preferably allowing an intravenous-to-oral switch to reduce the length of hospital stay and hospital-related costs.

Lefamulin is a pleuromutilin antimicrobial in late-stage clinical development for

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intravenous and oral use in patients with CABP. It is an inhibitor of bacterial protein synthesis by binding to the A and P sites of the peptidyl transferase center in the large subunit of the bacterial ribosome (16, 17). The unique interaction in this highly conserved region confers a low propensity for the development of bacterial resistance and is thought to be the reason for the lack of cross-resistance with other antibacterial classes, including macrolides, ketolides, lincosamides, fluoroquinolones, and tetracyclines (17). The antibacterial spectrum of lefamulin covers the typical Gram-positive and fastidious Gram-negative respiratory pathogens known to cause CABP and atypical pathogens, such as *M. pneumoniae* (including macrolide-resistant strains), *C. pneumoniae*, and *L. pneumophila* (18, 19). Pharmacokinetic and pharmacodynamic analyses demonstrated that lefamulin has rapid and predictable penetration into plasma (~1 to 2 μg/ml after a single 150-mg intravenous or 600-mg oral dose) (20) and target tissues, such as the epithelial lining fluid in the lung (21), reaching area under the concentration-time curve (AUC):MIC ratios that support the proposed tentative breakpoints of 1 μg/ml for *S. pneumoniae* and 0.5 μg/ml for *S. aureus* (22). This study evaluated the *in vitro* activity of lefamulin and comparators against a global collection of typical respiratory pathogens that commonly cause CABP, as collected by the SENTRY Antimicrobial Surveillance Program (2015 to 2016).

The activity of lefamulin and comparators were determined against 8,595 unique bacterial pathogens collected from 65 medical centers from North America (United States [34 states]; $n = 3,240$), 39 from Europe and the Mediterranean region (19 nations, including Turkey and Israel; $n = 3,362$), 15 from the Asia-Pacific region (7 nations; $n = 1,271$), and 10 from Latin America (4 nations; $n = 722$) and submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, IA, USA) for confirmation of bacterial identification (matrix-assisted laser desorption ionization–time of flight mass spectrometry [MALDI-TOF]) and susceptibility testing. Only 1 isolate per patient infection episode was included in the surveillance. All organisms were isolated from documented infections, including 4,667 (54.3%) community-acquired respiratory tract infections (3,124 *S. pneumoniae*, 930 *H. influenzae*, and 613 *M. catarrhalis* isolates), 2,036 (23.7%) pneumonia in hospitalized patients (276 *S. pneumoniae*, 1,585 *S. aureus*, 126 *H. influenzae*, and 49 *M. catarrhalis* isolates), 1,133 (13.2%) bloodstream infections (bacteremia; 370 *S. pneumoniae*, 737 *S. aureus*, 23 *H. influenzae*, and 3 *M. catarrhalis* isolates), 589 (6.9%) skin and skin structure infections (15 *S. pneumoniae*, 571 *S. aureus*, and 3. *H. influenzae* isolates), and 170 (2.0%) infections from other sites.

MICs for lefamulin and comparators were determined against *S. pneumoniae* ($n = 3,923$), *S. aureus* ($n = 2,919$), *H. influenzae* ($n = 1,086$), and *M. catarrhalis* ($n = 667$) strains from frozen-form MIC panels prepared by JMI Laboratories per Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods (23). Susceptibility and comparator categorical interpretations used breakpoint criteria from CLSI M100-S28 and European Committee on Antimicrobial Susceptibility Testing (2018), where available (24, 25). Cation-adjusted Mueller-Hinton broth was used for testing *S. aureus* and *M. catarrhalis* and was supplemented with 2.5% to 5% lysed horse blood for *S. pneumoniae*. *Haemophilus* test medium was used for *H. influenzae*.

Lefamulin demonstrated potent *in vitro* activity against this large contemporary collection of bacterial pathogens that commonly cause CABP. Lefamulin at $\leq$1 μg/ml, the proposed tentative susceptible breakpoint for *S. pneumoniae* based on clinical and nonclinical studies (22), inhibited 99.2% of all isolates tested, including 100% of *S. pneumoniae* isolates, 99.8% of *S. aureus* isolates, 93.8% of *H. influenzae* isolates, and 100% of *M. catarrhalis* isolates (Table 1). The activity of lefamulin against *S. pneumoniae*, the most frequently isolated bacterial CABP pathogen, was unaffected by resistance to other antibacterial classes, including β-lactams, fluoroquinolones, and macrolides as well as multidrug-resistant (MDR) or extensive drug-resistant strains; all $MIC_{50/90}$ values were 0.06/0.12 μg/ml, except among levofloxacin nonsusceptible isolates (0.06/0.25 μg/ml) (Table 1). Lefamulin was among the most potent agents tested and had the lowest $MIC_{50/90}$ values against MDR *S. pneumoniae* (0.06/0.12 μg/ml) (Table 1). Among comparators, *S. pneumoniae* isolates showed high rates of susceptibility ($\geq$98%) to

TABLE 1 Frequency of occurrence of lefamulin MICs for all pathogens tested

Organism (no. of isolates)	Cumulative % of isolates inhibited at lefamulin MIC (μg/ml) of:												MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8		
S. pneumoniae (3,923)	0.1	1.8	11.4	55.1	93.7	99.6	99.9	100.0					0.06	0.12
Penicillin nonsusceptible, nonmeningitis (≥4 μg/ml) (189)	0.0	1.1	7.9	64.0	98.4	100.0							0.06	0.12
Ceftriaxone nonsusceptible (≥2 μg/ml) (155)	0.0	0.6	10.3	63.9	99.4	100.0							0.06	0.12
Erythromycin nonsusceptible (≥0.5 μg/ml) (1,348)	0.2	2.2	12.4	52.9	93.1	99.0	99.7	100.0					0.06	0.12
Levofloxacin nonsusceptible (≥4 μg/ml) (47)	0.0	8.5	23.4	68.1	89.4	97.9	97.9	100.0					0.06	0.25
MDR[a] (821)	0.4	2.9	15.8	61.1	96.3	99.8	99.8	100.0					0.06	0.12
XDR[a] (181)	0.0	0.6	7.2	64.6	98.9	100.0							0.06	0.12
S. aureus (2,919)			26.0	88.9	99.2	99.6	99.7	99.8	99.8	99.8	99.8	100.0	0.06	0.12
Methicillin susceptible (1,981)			25.6	95.2	99.7	99.7	99.8	99.9	>99.9	>99.9	>99.9	100.0	0.06	0.06
Methicillin resistant (938)			26.9	75.7	98.2	99.4	99.5	99.6	99.7	99.8	99.8	100.0	0.06	0.12
H. influenzae (1,086)					1.7	20.4	69.4	93.8	99.1	99.9	100.0		0.5	1
β-lactamase negative (835)					1.9	20.0	67.5	93.2	98.9	100.0			0.5	1
β-lactamase positive (251)					1.2	21.9	75.7	96.0	99.6	99.6	100.0		0.5	1
M. catarrhalis (667)	1.0	2.4	11.1	88.3	99.9	100.0							0.06	0.12

[a]MDR and XDR status was based on nonsusceptibility to ≥3 and ≥5 classes, respectively, of the following antimicrobial agents, as described by Golden et al. (30) and applying the following breakpoints: penicillin (MIC, ≥4 μg/ml), ceftriaxone (MIC, ≥2 μg/ml), erythromycin (MIC, ≥0.5 μg/ml), clindamycin (MIC, ≥0.5 μg/ml), levofloxacin (MIC, ≥4 μg/ml), tetracycline (MIC, ≥2 μg/ml), and trimethoprim-sulfamethoxazole (MIC, ≥1 μg/ml). MDR, multidrug resistant; XDR, extensive drug resistant.

ceftaroline, levofloxacin, linezolid, moxifloxacin, and vancomycin (Table 2). Moderate resistance (range, 16.8% to 34.3%) was seen to erythromycin, azithromycin, tetracycline, trimethoprim-sulfamethoxazole, and clindamycin; among the 20.9% of MDR *S. pneumoniae* isolates, rates of resistance to these same agents were higher (range, 46.9% to 98.8%) (Table 2).

Lefamulin was also among the most active compounds against *S. aureus* ($MIC_{50/90}$, 0.06/0.12 μg/ml), including methicillin-resistant *S. aureus* (MRSA; $MIC_{50/90}$, 0.06/0.12 μg/ml) (Table 1 and 2). Among comparators, *S. aureus* isolates showed high rates of susceptibility (≥95%) to ceftaroline, doxycycline, linezolid, trimethoprim-sulfamethoxazole, and vancomycin (Table 2). High resistance rates were observed among MRSA isolates, particularly to macrolides (azithromycin, 75.5% to 76.2%) and fluoroquinolones (levofloxacin, 72.3% to 74.0%) (Table 2).

Lefamulin displayed potent activity against *H. influenzae*, including β-lactamase-positive isolates (all $MIC_{50/90}$, 0.5/1 μg/ml). Compared with the Gram-positive pathogens, the overall MIC distribution of lefamulin shifted to higher MIC values as observed for macrolide antibiotics. However, most *H. influenzae* isolates (93.8%), including β-lactamase negative (93.2%) and β-lactamase positive (96.0%), were inhibited at concentrations of ≤1 μg/ml (Table 1). *H. influenzae* isolates showed high rates of susceptibility (≥90%) to all comparator agents tested, with the exception of trimethoprim-sulfamethoxazole and ampicillin (Table 2). Resistance rates were high to trimethoprim-sulfamethoxazole (39.8% to 41.8%) and to ampicillin (99.6% to 100%) among β-lactamase-positive isolates, whereas resistance rates were lower among β-lactamase-negative isolates (trimethoprim-sulfamethoxazole, 28.3% to 30.3%; ampicillin, 2.9% to 9.3%).

All *M. catarrhalis* isolates were inhibited at lefamulin concentrations of ≤0.25 μg/ml ($MIC_{50/90}$, 0.06/0.12 μg/ml) (Table 1). *M. catarrhalis* isolates showed high rates of susceptibility (97.3% to 100%) to all comparators (Table 2). β-Lactamase activity was detected in 97% of tested isolates ($n = 335$).

Analysis of lefamulin results by infection type and by geographic region showed no

TABLE 2 Activity of lefamulin and comparators against pathogens commonly causing community-acquired bacterial pneumonia

Antibacterial agent by pathogen[a] (no. organisms tested)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	MIC range (μg/ml)	Susceptibility rates (%) according to: CLSI[b] S	I	R	EUCAST[b] S	I	R
S. pneumoniae									
Lefamulin (3,923)	0.06	0.12	≤0.008 to 1						
Amoxicillin-clavulanic acid (3,902)	≤0.03	2	≤0.03 to >4	93.6	2.9	3.5			
Azithromycin (3,921)	0.06	>4	≤0.03 to >4	65.7	0.7	33.6	65.3	0.4	34.3
Ceftaroline (3,905)	≤0.008	0.12	≤0.008 to >1	99.8			99.5		0.5
Ceftriaxone (3,905)	0.03	1	≤0.015 to >2	86.5	9.5	4.0[c]	86.5	12.5	0.9
				96.0	3.0	0.9[d]			
Clindamycin (3,906)	≤0.25	>1	≤0.25 to >1	82.7	0.5	16.8	83.2		16.8
Erythromycin (3,907)	0.03	>2	≤0.015 to >2	65.5	0.4	34.1	65.5	0.4	34.1
Levofloxacin (3,923)	1	1	≤0.12 to >4	98.8	0.1	1.1	98.8		1.2
Moxifloxacin (2,088[e])	0.12	0.25	≤0.03 to >4	98.9	0.5	0.6	98.8		1.2
Penicillin (3,923)	≤0.06	2	≤0.06 to >8	65.6	22.4	12.0[f]	65.6		34.4[c]
				65.6		34.4[g]	65.6	29.5	4.8[d]
				95.2	4.4	0.4[h]			
Tetracycline (3,922)	≤0.25	>4	≤0.25 to >4	76.7	0.5	22.8	76.7	0.5	22.8
Trimethoprim-sulfamethoxazole (3,921)	≤0.5	>4	≤0.5 to >4	71.2	10.8	18.1	77.8	4.2	18.1
MDR *S. pneumoniae*									
Lefamulin (821)	0.06	0.12	≤0.008 to 1						
Amoxicillin-clavulanic acid (820)	1	>4	≤0.03 to >4	74.1	11.7	14.1			
Azithromycin (821)	>4	>4	0.015 to >4	1.2	1.1	97.7	1.0	0.2	98.8
Ceftaroline (821)	0.06	0.25	≤0.008 to >1	99.3			97.8		2.2
Ceftriaxone (821)	0.5	2	≤0.015 to >2	55.8	25.8	18.4[c]	55.8	39.8	4.4
				81.6	14.0	4.4[d]			
Clindamycin (821)	>1	>1	≤0.25 to >1	22.4	1.8	75.8	24.2		75.8
Erythromycin (821)	>2	>2	≤0.015 to >2	0.6	0.6	98.8	0.6	0.6	98.8
Levofloxacin (821)	1	1	0.25 to >4	96.5	0.2	3.3	96.5		3.5
Moxifloxacin (427[e])	0.12	0.25	≤0.03 to >4	97.2	1.6	1.2	97.0		3.0
Penicillin (821)	1	4	≤0.06 to >8	16.3	41.4	42.3[f]	16.3		83.7[c]
				16.3		83.7[g]	16.3	62.1	21.6[d]
				78.4	19.5	2.1[h]			
Tetracycline (821)	>4	>4	≤0.25 to >4	4.5	1.1	94.4	4.5	1.1	94.4
Trimethoprim-sulfamethoxazole (821)	2	>4	≤0.5 to >4	32.9	20.2	46.9	45.3	7.8	46.9
S. aureus									
Lefamulin (2,919)	0.06	0.12	≤0.03 to >32						
Azithromycin (2,919)	0.5	>4	≤0.03 to >4	59.3	1.4	39.4	58.7	0.6	40.7
Ceftaroline (2,919)	0.25	1	≤0.06 to >8	95.0	4.8	0.1	95.0	4.8	0.1[i]
							95.0		5.0[j]
Clindamycin (2,919)	≤0.25	>2	≤0.25 to >2	85.8	0.2	14.0	85.5	0.3	14.2
Doxycycline (2,919)	≤0.06	0.25	≤0.06 to >8	97.9	2.0	0.1	95.1	0.9	4.0
Erythromycin (2,919)	0.25	>8	≤0.06 to >8	58.9	5.3	35.8	59.5	1.8	38.7
Levofloxacin (2,919)	0.25	>4	≤0.03 to >4	72.2	0.9	26.9	72.2		27.8
Linezolid (2,919)	1	1	≤0.12 to 8	>99.9		<0.1	>99.9		<0.1
Moxifloxacin (1,646[e])	≤0.06	4	≤0.06 to >4	73.4	7.5	19.1	73.0		27.0
Oxacillin (2,919)	0.5	>2	≤0.25 to >2	67.9		32.1	67.9		32.1
Trimethoprim-sulfamethoxazole (2,919)	≤0.5	≤0.5	≤0.5 to >4	98.2		1.8	98.2	0.2	1.6
Vancomycin (2,919)	0.5	1	≤0.12 to 2	100.0	0.0	0.0	100.0		0.0
MRSA									
Lefamulin (938)	0.06	0.12	≤0.03 to >32						
Azithromycin (938)	>4	>4	0.06 to >4	23.8	0.7	75.5	23.3	0.4	76.2
Ceftaroline (938)	1	2	0.25 to >8	84.5	15.0	0.4	84.5	15.0	0.4[i]
							84.5		15.5[j]
Clindamycin (938)	≤0.25	>2	≤0.25 to >2	62.0	0.0	38.0	61.9	0.1	38.0
Doxycycline (938)	≤0.06	2	≤0.06 to >8	94.5	5.3	0.2	89.4	1.4	9.2
Erythromycin (938)	>8	>8	≤0.06 to >8	23.3	4.7	72.0	23.8	1.2	75.1
Levofloxacin (938)	>4	>4	0.06 to >4	26.0	1.7	72.3	26.0		74.0
Linezolid (938)	1	1	≤0.12 to 2	100.0		0.0	100.0		0.0
Moxifloxacin (536[e])	2	>4	≤0.06 to >4	29.7	18.5	51.9	28.7		71.3
Oxacillin (938)	>2	>2	>2 to >2	0.0		100.0	0.0		100.0
Trimethoprim-sulfamethoxazole (938)	≤0.5	≤0.5	≤0.5 to >4	94.9		5.1	94.9	0.6	4.5
Vancomycin (938)	0.5	1	≤0.12 to 2	100.0	0.0	0.0	100.0		0.0

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TABLE 2 (Continued)

Antibacterial agent by pathogen[a] (no. organisms tested)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	MIC range (μg/ml)	Susceptibility rates (%) according to: CLSI[b] S	CLSI I	CLSI R	EUCAST[b] S	EUCAST I	EUCAST R
H. influenzae									
Lefamulin (1,086)	0.5	1	≤0.12 to 8						
Amoxicillin-clavulanic acid (1,086)	0.5	2	≤0.12 to >8	98.0		2.0	94.3		5.7
Ampicillin (1,086)	0.5	>8	0.12 to >8	69.7	5.1	25.2	69.7		30.3
Azithromycin (1,086)	1	1	0.12 to >4	98.8			98.8[k]		
Cefepime (1,086)	0.06	0.25	≤0.015 to >2	99.8			96.6		3.4
Ceftriaxone (1,086)	≤0.015	≤0.015	≤0.015 to 0.5	100.0			98.5		1.5
Clarithromycin (1,086)	8	8	0.25 to >16	91.9	6.4	1.7	100.0[k]		
Levofloxacin (1,086)	≤0.015	0.03	≤0.015 to >2	99.6			98.2		1.8
Moxifloxacin (550[e])	0.03	0.03	0.008 to >1	99.6			98.9		1.1
Tetracycline (1,086)	0.5	0.5	≤0.12 to >8	98.3	0.1	1.6	98.2	0.2	1.7
Trimethoprim-sulfamethoxazole (1,086)	0.12	>4	≤0.06 to >4	65.7	3.4	30.9	65.7	1.4	33.0
M. catarrhalis									
Lefamulin (667)	0.06	0.12	≤0.008 to 0.25						
Amoxicillin-clavulanic acid (667)	0.12	0.25	≤0.06 to 0.5	100.0		0.0	100.0		0.0
Azithromycin (662)	0.015	0.03	0.002 to 0.06	100.0			100.0	0.0	0.0
Ceftriaxone (667)	0.25	0.5	≤0.015 to 2	100.0			99.7	0.3	0.0
Clarithromycin (662)	≤0.12	≤0.12	≤0.12 to 0.25	100.0			100.0	0.0	0.0
Erythromycin (662)	0.12	0.12	≤0.015 to 1	100.0			98.9	0.8	0.3
Levofloxacin (667)	0.03	0.06	≤0.015 to 1	100.0			99.4		0.6
Moxifloxacin (221[e])	0.06	0.06	0.03 to 0.5				99.5		0.5
Tetracycline (667)	0.25	0.25	≤0.03 to 0.5	100.0	0.0	0.0	100.0	0.0	0.0
Trimethoprim-sulfamethoxazole (667)	0.12	0.25	≤0.06 to 2	97.3	2.7	0.0	97.3	2.1	0.6

[a]MDR, multidrug resistant; MRSA, methicillin-resistant *S. aureus*.
[b]Criteria as published by CLSI 2018 and EUCAST 2018. CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; I, intermediate; R, resistant; S susceptible.
[c]Using meningitis breakpoints.
[d]Using nonmeningitis breakpoints.
[e]Moxifloxacin was tested in 2016 but not in 2015.
[f]Using oral breakpoints.
[g]Using parenteral, meningitis breakpoints.
[h]Using parenteral, nonmeningitis breakpoints.
[i]Using other than pneumonia breakpoints.
[j]Using pneumonia breakpoints.
[k]Percentage of wild type based on epidemiological cutoff value. EUCAST version 8.0 (2018).

apparent differences across isolate sources and across Asia-Pacific, Europe, Latin America, or North America.

Our results are consistent with previous studies reporting on the *in vitro* activity of lefamulin against typical and atypical respiratory pathogens (e.g., *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila*) (18, 19, 26, 27). Furthermore, the *in vitro* activity of lefamulin has translated to clinical efficacy in two phase 3 clinical trials in adults with CABP, demonstrating the noninferiority of 5 to 10 days of lefamulin versus 7 to 10 days of moxifloxacin given in intravenous-to-oral or oral administration (28, 29).

In conclusion, lefamulin was highly active against pathogens commonly causing CABP collected globally between 2015 and 2016, with activity consistent across geographic regions and unaffected by resistance to other antibacterial classes. These data support the ongoing clinical development of lefamulin for the treatment of CABP and other respiratory tract infections.

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