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In Vitro Activity of Lefamulin against Staphylococccus aureus from Hospital-Acquired Pneumonia (HAP) and Community-Acquired Pneumonia (CAP) Patients in Europe

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Background: Lefamulin is the first semi-synthetic pleuromutilin antibiotic for IV and oral use in humans. Lefamulin inhibits bacterial protein synthesis by binding to the A- and P-site of the peptidyl transferase centre of the 50S ribosomal preventing the correct positioning of the CCA-ends of tRNA. Lefamulin is currently in Phase 3 trials for the treatment of CAP in adults.

HAP is the second most common nosocomial bacterial infection and the primary cause of death among nosocomial infections, particularly in intensive care units. *S. aureus* is a well-recognized pathogen causing up to 40% of HAP and treatment is challenging due to growing resistance rates.

This study investigated the susceptibility of *S. aureus* strains to lefamulin and comparators collected from HAP and hospitalized CAP patients in Europe in 2015.

Material/methods: 217 unique hospital-acquired (HA-SA) and 180 unique community-acquired *S. aureus* (CA-SA) isolates were collected from pneumonia patients from 19 European countries (32 sites) in 2015 as part of the SENTRY surveillance project. Susceptibility testing was conducted using the CLSI broth microdilution method, and susceptibility was calculated using EUCAST 2016 breakpoints.

Results: Lefamulin was the most potent compound tested, with 100% of HA-SA and CA-SA isolates inhibited at a concentration of ≤0.25 mg/L and ≤0.12 mg/L, respectively. Susceptibility to lefamulin was similar for both subsets and was unaffected by resistance to the other antibiotics tested. Among HAP isolates, 24.4% were MRSA which was slightly higher than for CAP strains (21.7%). The susceptibility of HA-SA to macrolides was higher (70.5%) than for HA-MRSA (37.7%). 92.6% of HA-SA and 95.0 % of CA-SA were susceptible to ceftaroline (HA-MRSA 69.8% and CA-MRSA 76.9%), while all MRSA were fully susceptible to linezolid and vancomycin.

Conclusions: Lefamulin displayed potent activity against *S. aureus* isolates collected from HAP and CAP patients irrespective of their resistance phenotypes. These data support the development of lefamulin for infections caused by *S. aureus*, including ABSSI, CAP and HAP.

Table: Antibacterial activity of lefamulin and comparators against *S. aureus* from HAP and CAP patients

	HAP (*n*=217)			CAP (*n*=180)		
	$MIC_{50/90}$	**%S**	**%R**	**$MIC_{50/90}$**	**%S**	**%R**
Lefamulin	0.06/0.12	-	-	0.06/0.06	-	-
Azithromycin	0.5/>4	70.5	29.5	0.5/>4	60.6	39.4
Ceftaroline	0.25/1	92.6	7.4	0.25/1	95.0	5.0
Clindamycin	≤0.25/≤0.25	93.5	6.5	≤0.25/0.5	89.4	10.0
Levofloxacin	0.25/ >4	76.0	24.0	0.25/>4	78.3	21.7
Linezolid	1/1	99.5	0.5	1/1	100.0	0.0
Oxacillin	0.5/>2	75.6	24.4	0.5/>2	78.3	21.7
Vancomycin	0.5/1	100.0	0.0	0.5/1	100.0	0.0