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In Vitro Activity of Lefamulin against S. aureus Collected from Hospitalized Patients with Bacterial Pneumonia in Europe

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Background: Lefamulin is the first semi-synthetic pleuromutilin antibiotic for IV and oral use in humans. Pleuromutilins specifically inhibit bacterial protein synthesis by binding to the A- and P-site of the peptidyl transferase centre ("induced fit"). Lefamulin was shown to be highly active in the lung *in vivo* and to be unaffected by the presence of surfactant. Furthermore, it has been well tolerated in phase 1 and 2 trials. Lefamulin is currently in Phase 3 trials for the treatment of community-acquired bacterial pneumonia (CAP) in adults. *S. aureus* is a well-recognized cause of pneumonia from both the community and hospital setting. The clinical management of staphylococcal pneumonia is complicated by the high prevalence of methicillin-resistance observed in *S. aureus* (MRSA) and the invasive infection it causes.

This study investigated the susceptibility of *S. aureus* strains collected from patients hospitalized with pneumonia in Europe in 2015 to lefamulin and comparators commonly used to treat CAP.

Material/methods: 510 unique *S. aureus* isolates were collected from hospitalized patients with pneumonia in 19 European countries (33 sites) in 2015 as part of the SENTRY surveillance program. Susceptibility testing was conducted using the CLSI broth microdilution method and susceptibility was interpreted per EUCAST 2016 breakpoint criteria.

Results: Lefamulin was the most potent compound tested, with 99.8% of all isolates being inhibited at a concentration of ≤0.25 mg/L ($MIC_{50/90}$ values of 0.06/0.06 mg/L). Susceptibility rates were >90% (Table) for clindamycin ($MIC_{50/90}$, ≤0.25 mg/L), vancomycin ($MIC_{50/90}$, 0.5/1 mg/L), linezolid ($MIC_{50/90}$, 1 mg/L), and ceftaroline ($MIC_{50/90}$, 0.25/1 mg/L). 21% of isolates (*n*=107) were oxacillin-resistant (MRSA), all of which were inhibited by lefamulin (MIC range, ≤0.03-0.25 mg/L; $MIC_{50/90}$, 0.06/0.12 mg/L), vancomycin, and linezolid, while MRSA strains showed limited susceptibility to azithromycin (72.9%resistant), levofloxacin (88.8% resistant), clindamycin (30.8% resistant), and ceftaroline (24.3 % resistant).

Conclusions: *S. aureus* strains collected from patients hospitalized with pneumonia were highly susceptible to lefamulin regardless of susceptibility phenotype to the other antibiotics tested. Due to its potent activity against resistant *S. aureus* and the most prevalent typical and atypical respiratory pathogens, as well as the availability of IV and oral formulations, lefamulin has the potential to play a role in the empiric treatment of CAP.

Table: Antibacterial activity of lefamulin and comparators against *n*=510 *S. aureus* strains [mg/L]

Compound	MIC_{50}	MIC_{90}	MIC_{99}	%S	%R
Lefamulin	0.06	0.06	0.12	-	-
Azithromycin	0.5	>4	>4	68.8	31.2
Ceftaroline	0.25	1	2	94.9	5.1
Clindamycin	≤0.25	≤0.25	>2	91.8	7.6
Levofloxacin	0.25	>4	>4	78.2	21.8
Oxacillin	0.5	>2	>2	79.0	21.0
Linezolid	1	1	1	99.8	0.2
Vancomycin	0.5	1	1	100.0	0.0