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In Vitro Activity of Lefamulin against *S. aureus* from Hospital-Acquired Pneumonia (HAP) And Community-Acquired Pneumonia (CAP) Patients in Europe

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INTRODUCTION & PURPOSE

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.[1,2] Lefamulin is currently in Phase 3 trials for the treatment of CAP in adults. Its antibacterial profile covers the most important Gram-positive, fastidious Gram-negative and atypical bacterial pathogens causing pneumonia.[3-5]

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.[6,7]

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

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 countries including Belarus, Belgium, Czech Republic, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Poland, Portugal, Romania, Russia, Slovenia, Spain, Sweden, Turkey and United Kingdom (32 sites) in 2015 as part of the SENTRY surveillance project. Only one isolate per patient infection episode was included in surveillance. For this investigation, a *S. aureus* isolate obtained from an outpatient or earlier than 48 hours after hospitalization was considered community-acquired (CAP), whereas *S. aureus* isolates obtained later than 48 hours after hospitalization were considered hospital-acquired (HAP). [8]

Susceptibility testing was conducted using the CLSI broth microdilution method and susceptibility was calculated using EUCAST 2017 breakpoints.[8,9] QC reference organisms were tested concurrently for lefamulin and comparator agents.

Table 1. Antibacterial activity of lefamulin and comparators against *S. aureus* (MSSA and MRSA) from HAP and CAP patients

	HAP (*n*=217)				CAP (*n*=180)			
	MIC_{50}	MIC_{90}	%S	%R	MIC_{50}	MIC_{50}	%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

[a], Criteria as published by EUCAST [2017]; **bold and underlined %,** resistance rate ≥10%

RESULTS

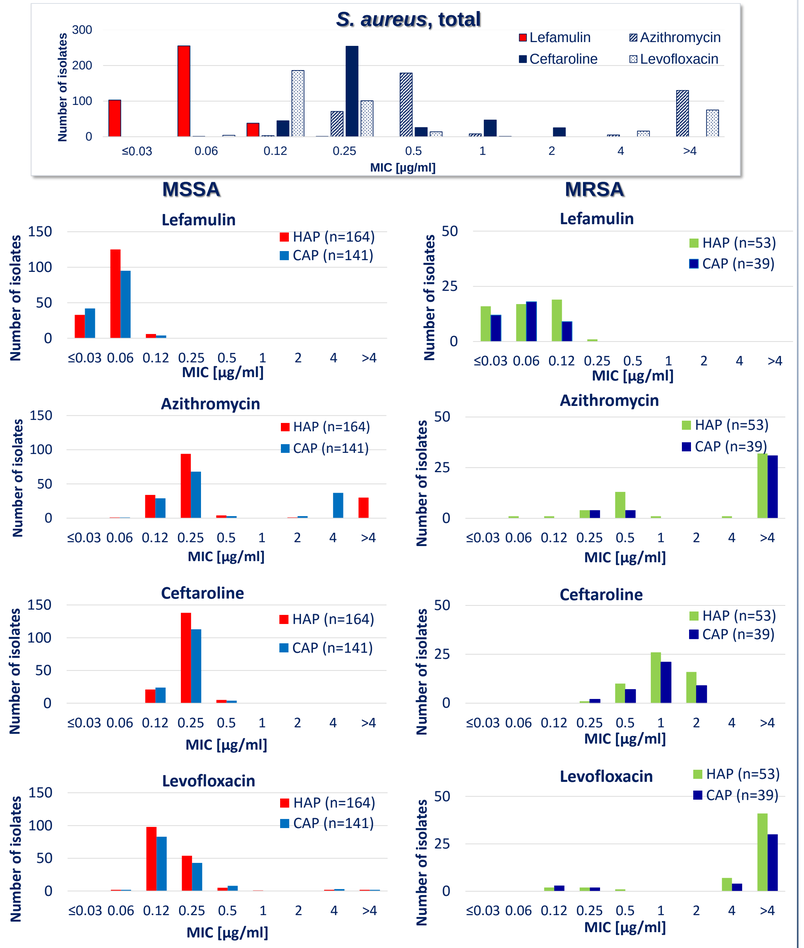

Figure 1. MIC distributions of lefamulin and comparators

RESULTS (continued)

- 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, hospital-acquired and community acquired isolates (Table 1 and Figure 1).
- The lefamulin activity was unaffected by resistance to the other antibiotics tested including macrolides, fluoroquinolones, tetracyclines and others.
- Among HAP isolates, 24.4% were MRSA which was slightly higher than for CAP strains (21.7%). HAP and CAP isolates showed overall similar MIC distributions and susceptibility rates for lefamulin and comparators with the exception of azithromycin
  - 79.5% of CA-MRSA but only 37.7% of HA-MRSA were resistant to azithromycin.
- MRSA showed higher resistance rates to azithromycin, ceftaroline or lefofloxacin than MSSA.
  - 71.6% CA-MSSA and 81.1% of HA-MSSA were susceptible to azithromycin.
  - Only 9.4% of HA-MRSA and 12.8% of CA-MRSA were susceptible to levofloxacin, whereas 97.6% HA-MSSA and 96.5% of CA-MSSA were susceptible to levofloxacin.
  - 69.8% HA-MRSA and 76.9% CA-MRSA were susceptible to ceftaroline, while 100% of HA-MSSA of CA-MSSA were susceptible.
- All MSSA and MRSA were fully susceptible to vancomycin and only 1 isolate was resistant to linezoid.

CONCLUSIONS

- **Lefamulin displayed potent activity against *S. aureus* isolates collected from HAP and CAP patients including MRSA and MSSA irrespective of their resistance phenotypes.**
- **HAP and CAP isolates showed similar susceptibility rates, with MRSA displaying higher resistance to macrolides, levofloxacin and ceftaroline than MSSA.**
- **These data support the development of lefamulin for infections caused by *S. aureus*, including CAP, HAP and acute bacterial skin and skin structure infections (ABSSSI).**

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