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Lefamulin Activity against a Contemporary Global Collection of *Staphylococcus aureus* (SENTRY 2020–2021)

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INTRODUCTION

- Lefamulin is a first-in-class, oral and IV pleuromutilin antibiotic approved in the United States (US), Europe (EU), and Canada for the treatment of community-acquired pneumonia (CAP) in adults caused by susceptible typical and atypical bacterial organisms, including *S. aureus*.[1]
- Lefamulin inhibits bacterial protein synthesis via a unique mechanism of action and its potency against *S. aureus* has been well established *in vitro*, *in vivo*, and in phase 3 clinical trials in patients with CAP and *S. aureus* identified as the causative organism at baseline.[2–5]
- Lefamulin has further demonstrated potent efficacy in a phase 2 clinical trial for the treatment of patients with ABSSSI (>80% cellulitis or abscess with cellulitis) caused by gram-positive pathogens including MRSA and methicillin-susceptible *S. aureus* that was comparable to that of vancomycin.[6]
- Although there are various antibiotic treatment options available, *S. aureus*, and particularly methicillin-resistant *S. aureus* (MRSA), remains a major cause of healthcare-associated infections in Europe and is identified by the CDC as a "serious threat" (Figure 1).[7–11]
- The need for alternative treatment options is driven by resistance, adverse events, contraindicated drug class, or concerns of renal toxicity.
- We evaluated the *in vitro* activity of lefamulin against *S. aureus* collected globally via the SENTRY Program in 2020–2021.

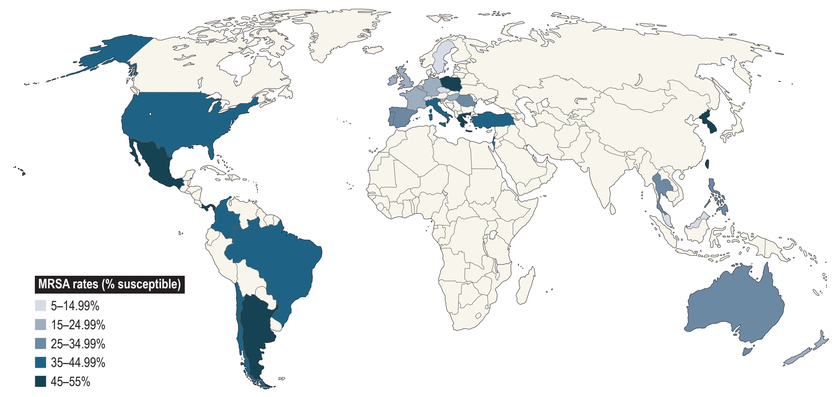
MATERIALS AND METHODS

- A total of 5,028 *Staphylococcus aureus* were collected from 85 medical centres in 2020–2021 as follows:
  - EU: 1,829 isolates from 35 medical centres located in 18 countries
  - US: 2,543 isolates from 31 medical centres
  - Asia-Pacific region (APAC): 373 isolates from 12 medical centres in 7 countries
  - Latin America (LATAM): 283 isolates from 7 medical centres in 5 countries
- Isolates were from infections of the respiratory tract (22.2%, including CABP [9.9%]), bloodstream (25.6%), skin and soft tissue (44.9%), and other body sites (7.3%).
- Susceptibility testing was performed by CLSI broth microdilution reference methods and EUCAST breakpoints were applied.[12, 13]

RESULTS

- Lefamulin was highly active against the *S. aureus* collection across all geographic regions ($MIC_{50/90}$, 0.06/0.12 mg/L), with 99.7% of isolates inhibited at ≤0.25 mg/L, consistent with the susceptible breakpoint published by EUCAST and CLSI (Table 1 and Figures 2 to 4).
- Limited variation, no more than 1 $\log_2$ dilution, was observed in lefamulin $MIC_{50/90}$ values for all regions (data not shown).
- Lefamulin was active against methicillin-resistant (R) *S. aureus* (MRSA), with an $MIC_{50/90}$ of 0.06/0.12 mg/L and 99.3% susceptibility (Table 1 and Figures 3 and 4).
- Lefamulin activity was unaffected by other resistance phenotypes, such as (Table 1 and Figure 4):
  - Azithromycin-nonsusceptible (NS): $MIC_{50/90}$ of 0.06/0.12 mg/L and 99.7%S
  - Ceftaroline-R: $MIC_{50/90}$ of 0.12/0.25 mg/L and 98.5%S
  - Clindamycin-NS: $MIC_{50/90}$ of 0.06/0.12 mg/L and 98.0%S
  - Doxycycline-NS: $MIC_{50/90}$ of 0.06/0.12 mg/L and 98.5%S
  - Gentamicin-R: $MIC_{50/90}$ of 0.06/0.12 mg/L and 99.5%S
  - Levofloxacin-R: $MIC_{50/90}$ of 0.06/0.12 mg/L and 99.1%S
  - Trimethoprim-sulfamethoxazole-NS: $MIC_{50/90}$ of 0.06/0.12 mg/L and 100.0%S
- MRSA susceptibilities to azithromycin, ceftaroline, and moxifloxacin were 24.2%, 90.5%, and 38.9%, respectively.

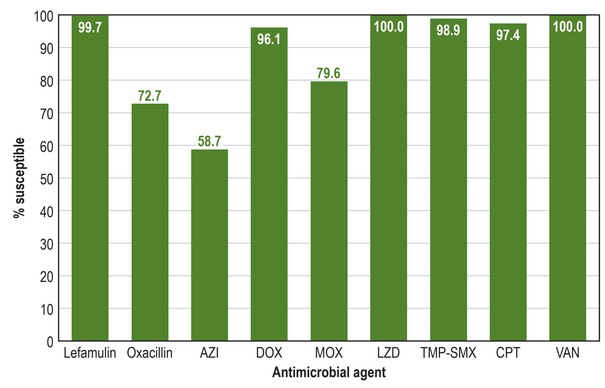
Figure 1. MRSA rates in countries surveyed by the SENTRY Program (*n*=13,911 isolates; 2020–2021)



CONCLUSIONS

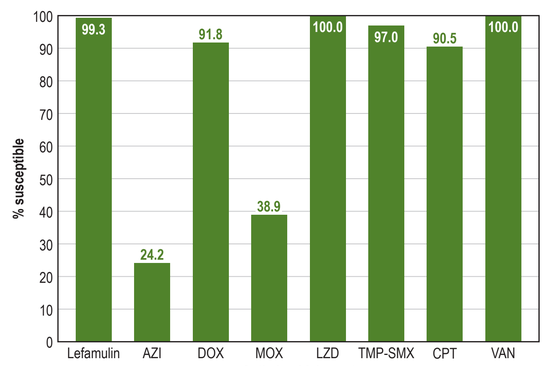
- Lefamulin demonstrated potent *in vitro* antibacterial activity against *S. aureus* including MRSA collected from patients worldwide regardless of geographic region and resistance phenotype.
- Lefamulin represents a valuable empiric treatment option for ambulatory and hospitalized patients with CAP, including those infected with *S. aureus.*
- Further studies are warranted to investigate the efficacy of lefamulin in other *S. aureus* infections.

Figure 2. Antimicrobial susceptibility of *S. aureus* collected worldwide (2020–2021)



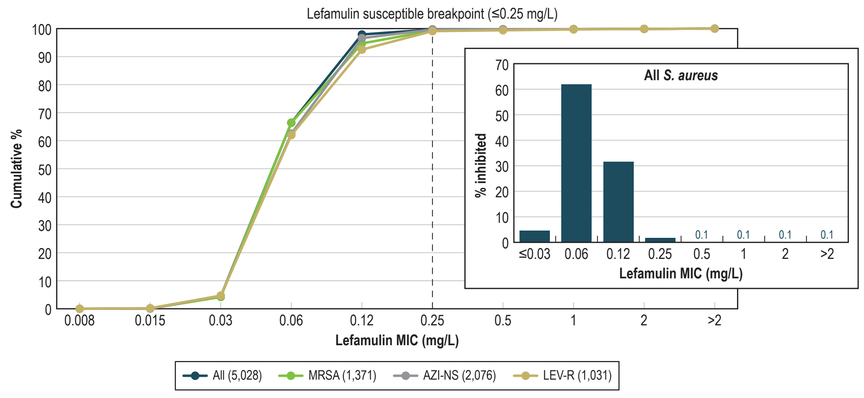
Abbreviations: AZI, azithromycin; DOX, doxycycline; MOX, moxifloxacin; LZD, linezolid; TMP-SMX, trimethoprim-sulfamethoxazole; CPT, ceftaroline; VAN, vancomycin.

Figure 3. Antimicrobial susceptibility of MRSA isolates collected worldwide (2020–2021)



Abbreviations: AZI, azithromycin; DOX, doxycycline; MOX, moxifloxacin; LZD, linezolid; TMP-SMX, trimethoprim-sulfamethoxazole; CPT, ceftaroline; VAN, vancomycin.

Figure 4. Lefamulin activity (cumulative MIC distributions) against *S. aureus* resistant subsets



Abbreviations: MRSA, methicillin-resistant *S. aureus*; AZI, azithromycin; NS, nonsusceptible per EUCAST; LEV, levofloxacin; R, resistant per EUCAST.

Table 1. Antimicrobial susceptibility of *S. aureus* stratified by resistance phenotype

Resistant subset (no.)	$MIC_{50/90}$ in mg/L (% Susceptible)					
	Lefamulin	Azithromycin	Doxycycline	Moxifloxacin	Linezolid	Vancomycin
All *S. aureus* (5,028)	0.06 / 0.12 (99.7)	1 / >8 (58.7)	≤0.06 / 0.25 (96.1)	≤0.06 / 2 (79.6)	1 / 2 (100.0)	1 / 1 (100.0)
MRSA (1,371)	0.06 / 0.12 (99.3)	>8 / >8 (24.2)	≤0.06 / 1 (91.8)	2 / >4 (38.9)	1 / 2 (100.0)	1 / 1 (100.0)
Azithromycin-NS (2,076)	0.06 / 0.12 (99.7)	>8 / >8 (0.0)	≤0.06 / 0.5 (93.9)	≤0.06 / >4 (60.8)	1 / 2 (100.0)	1 / 1 (100.0)
Clindamycin-NS (441)	0.06 / 0.12 (98.0)	>8 / >8 (1.4)	≤0.06 / 8 (83.4)	4 / >4 (23.4)	1 / 2 (100.0)	1 / 1 (100.0)
Ceftaroline-R (130)	0.12 / 0.25 (98.5)	>8 / >8 (5.4)	0.12 / 8 (84.6)	>4 / >4 (0.8)	1 / 2 (100.0)	1 / 1 (100.0)
Doxycycline-NS (198)	0.06 / 0.12 (98.5)	>8 / >8 (36.4)	4 / 8 (0.0)	0.12 / >4 (55.1)	1 / 2 (100.0)	1 / 1 (100.0)
Gentamicin-R (196)	0.06 / 0.12 (99.5)	>8 / >8 (45.4)	≤0.06 / 4 (84.2)	≤0.06 / >4 (61.5)	1 / 2 (100.0)	1 / 1 (100.0)
Levofloxacin-R (1,031)	0.06 / 0.12 (99.1)	>8 / >8 (21.0)	≤0.06 / 1 (91.4)	2 / >4 (0.5)	1 / 2 (100.0)	1 / 1 (100.0)
TMP-SMX-NS (54)	0.06 / 0.12 (100.0)	>8 / >8 (25.9)	≤0.06 / 8 (64.8)	2 / >4 (13.0)	1 / 1 (100.0)	1 / 1 (100.0)

Abbreviations: MRSA, methicillin-resistant *S. aureus*; NS, nonsusceptible per EUCAST criteria; R, resistant per EUCAST criteria; TMP-SMX, trimethoprim-sulfamethoxazole.

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