Poster# 333

Regional Analysis of Resistance Phenotypes among *Staphylococcus aureus* Causing Infections in US Census Divisions: Telavancin Activity against Resistant Pathogens (2014–2016)

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ABSTRACT

Background. Telavancin (TLV) is approved in the United States (US) for the treatment of complicated skin and skin structure infections (cSSSI) and hospital-acquired and ventilator-associated bacterial pneumonia caused by susceptible (S) *S. aureus* (SA) isolates when other alternatives are not suitable. This longitudinal study evaluated TLV activity and comparator resistance trends against SA isolates collected in the US from 2014 to 2016.

Methods. A total of 15,882 US clinical isolates were collected from 82 sites located in 37 states. Isolates were principally from cSSSI (51.1%), pneumonia in hospitalized patients (27.6%), and bloodstream infections (14.4%). Isolates were tested for S by CLSI methods, and MIC interpretations used CLSI criteria. Methicillin-resistant SA (MRSA) resistant to ≥3 additional drug classes were considered multidrug-resistant (MDR). The drugs used to assess MDR status were: clindamycin (CLI), daptomycin (DAP), erythromycin (ERY), gentamicin (GEN), levofloxacin (LEVO), linezolid (LZD), tetracycline (TET), and trimethoprim-sulfamethoxazole (TMP-SMX).

Results. All SA were S to TLV at the current CLSI breakpoint (≤0.12 µg/mL), and all TLV MIC_{90} values were 0.03–0.06 µg/mL, regardless of year, census division, or MDR phenotype. TLV MIC_{0290} values (0.03/0.06 µg/mL) were at least 8-fold lower than corresponding values for DAP (0.25/0.5 µg/mL), LZD (1/1 µg/mL), and vancomycin (VAN; 0.5/1 µg/mL) against SA. No VAN-resistant SA isolates were detected. Overall S rates were: CLI (84.4%), DAP (99.9%), ERY (41.3%), GEN (97.6%), LEVO (62.1%), LZD (>99.9%), TET (95.5%), and TMP-SMX (98.2%), and no significant changes were observed over the 3 years. MRSA rates declined overall (from 46.8% to 43.6%). MDR MRSA increased from 27.3% (2014) to 30.2% (2016). All DAP-nonsusceptible and LZD-R isolates exhibited MIC values of ≤0.06 µg/mL; the TLV MIC_{50} value for isolates with elevated VAN MICs (2 µg/mL; 0.4% of all SA) was 0.12 µg/mL.

Conclusions. TLV exhibited potent *in vitro* activity against SA (including MDR) from all US census divisions, with MIC_{0290} values at least 8-fold more potent than comparator values. Resistance rates for most comparators remained steady, the MRSA rate fell, and the MDR MRSA rate increased during the study period.

INTRODUCTION

- Telavancin (TLV) is a once-daily parenteral bactericidal lipoglycopeptide antimicrobial agent
- TLV was shown to be non-inferior to vancomycin in Phase 3 clinical trials of adult patients with complicated skin and skin structure infections (cSSSI) and with hospital-acquired bacterial pneumonia (HABP), including ventilator-associated bacterial pneumonia (VABP), due to susceptible gram-positive pathogens and *Staphylococcus aureus*
- TLV is approved in the United States (US) to treat cSSSI and HABP/VABP caused by susceptible *S. aureus* isolates when other alternatives are not suitable with or without concurrent bacteremia
- A Phase 3 multicenter randomized open-label noninferiority trial of telavancin versus standard IV therapy control (eg, vancomycin, daptomycin, anti-staphylococcal penicillin, or cefazolin) in the treatment of subjects with complicated *S. aureus* bacteremia and *S. aureus* right-sided infective endocarditis is being conducted
- This longitudinal study evaluated TLV activity and comparator resistance trends against *S. aureus* isolates collected in all US Census Bureau divisions from 2014 to 2016

MATERIALS AND METHODS

Bacterial strain collection

- A total of 15,882 US clinical isolates were collected from 82 sites located in 37 states and all 9 US Census Bureau divisions
- Isolates were principally from cSSSI (51.1%), pneumonia in hospitalized patients (27.6%), and bloodstream infections (14.4%; **Figure 1**)

Antimicrobial susceptibility test methods and MDR definition

- Isolates were tested for susceptibility by CLSI methods (document M07-A10), and MIC interpretations used CLSI criteria (document M100-S27)
- TLV broth microdilution MIC testing followed the CLSI-approved method supplemented with 0.002% polysorbate-80
- Bacterial inoculum density was monitored by colony counts to ensure an adequate number of cells for each testing event
- MIC values were validated by concurrently tested CLSI-recommended quality control reference strains (*S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212)
- Methicillin-resistant *S. aureus* (MRSA) isolates resistant to ≥3 additional drug classes were considered multidrug-resistant (MDR)
  - The drugs used to assess MDR status were: clindamycin, daptomycin (nonsusceptible isolates were scored as resistant), erythromycin, gentamicin, levofloxacin, linezolid, tetracycline, and trimethoprim-sulfamethoxazole (TMP-SMX)

RESULTS

- All *S. aureus* were susceptible to TLV at the current CLSI breakpoint (≤0.12 µg/mL; **Table 1** and **Figure 2**)
- All TLV MIC_{90} values were 0.03–0.06 µg/mL, regardless of year, infection type, census division, oxacillin resistance phenotype, or MDR phenotype (**Figure 2** and data not shown)
- Overall TLV MIC_{0290} values (0.03/0.06 µg/mL) were at least 8-fold lower than corresponding values for daptomycin (0.25/0.5 µg/mL), linezolid (1/1 µg/mL), and vancomycin (0.5/1 µg/mL) against *S. aureus* (**Table 1**)
  - No vancomycin-resistant isolates were detected
- Overall susceptibility rates were (**Table 1**): clindamycin (84.4%), daptomycin (99.9%), erythromycin (41.3%), gentamicin (97.6%), levofloxacin (62.1%), linezolid (>99.9%), tetracycline (95.5%), TMP-SMX (98.2%), and vancomycin (100.0%)
  - No large changes in drug susceptibilities were observed over the 3 years for the full isolate set or the MDR MRSA subset (**Figure 3**)
- MRSA rates declined overall (from 46.8% to 43.6%; **Figure 4**)
- Rates of the MDR phenotype among MRSA isolates increased from 27.3% (2014) to 30.2% (2016; **Figure 4**)
- Differences in MRSA and MDR MRSA rates were observed among the 9 US Census Bureau divisions (eg, compare MRSA rates between division 1 and 6; **Figure 4**)
- All TLV MIC values for daptomycin nonsusceptible (n = 8) and linezolid-resistant isolates (n = 5) were ≤0.06 µg/mL (data not shown)
- As observed previously, TLV MIC_{50} values increased with increasing vancomycin MIC values (**Figure 5**)
  - All isolates remained susceptible to TLV regardless of vancomycin MIC

Table 1. Activity of telavancin and comparator antimicrobial agents against 15,882 US isolates of *S. aureus* (2014–2016)

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a]		
				%S	%I	%R
Telavancin	0.03	0.06	≤0.015 — 0.12	100.0		
Clindamycin	≤0.25	>2	≤0.25 — >2	84.4	0.3	15.3
Daptomycin	0.25	0.5	≤0.12 — 4	99.9		
Erythromycin	>8	>8	≤0.12 — >8	41.3	6.0	52.7
Gentamicin	≤1	≤1	≤1 — >8	97.6	0.2	2.3
Levofloxacin	0.25	>4	≤0.12 — >4	62.1	1.1	36.8
Linezolid	1	1	≤0.12 — >8	>99.9		<0.1
Oxacillin	1	>2	≤0.25 — >2	54.9		45.1
Tetracycline	≤0.5	≤0.5	≤0.5 — >8	95.5	0.7	3.8
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 — >4	98.2		1.8
Vancomycin	0.5	1	≤0.12 — 2	100.0	0.0	0.0

[a]Criteria as published by CLSI (2017)

Figure 1. Infection types of tested *S. aureus* isolates

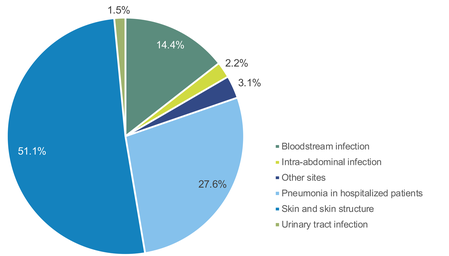


Figure 2. Telavancin MIC distributions by year

Figure 3. Susceptibility of *S. aureus* to telavancin and comparator agents stratified by year

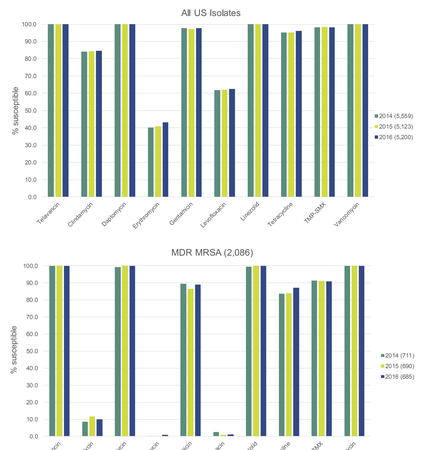


Figure 4. MRSA and MDR MRSA resistance trends by US Census Bureau division

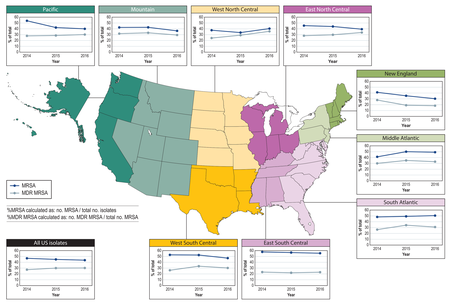
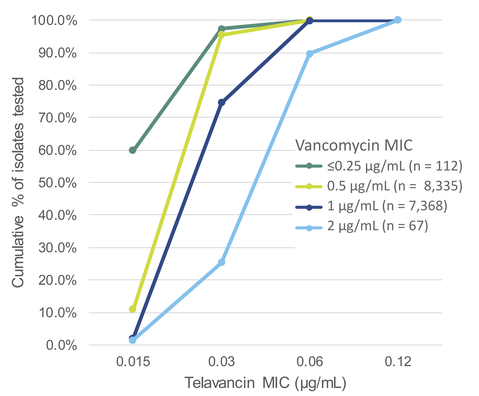


Figure 5. Telavancin activity against all *S. aureus* isolates stratified by vancomycin MIC (2014–2016)



CONCLUSIONS

- TLV exhibited potent *in vitro* antimicrobial activity against *S. aureus* isolates (including MDR MRSA) from all 9 US census divisions across all 3 surveyed years (100% susceptible)
- TLV MIC_{0290} values were at least 8-fold more potent than comparator values
- Overall resistance rates for most comparators remained steady, and although the overall MRSA rate fell consistently, the rates for the MDR phenotype within the MRSA population increased during the study period, which emphasizes the need for additional therapeutic options

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