Activity of Telavancin against a Contemporary Collection of *Staphylococcus aureus* Clinical Isolates from All 9 US Census Bureau Divisions

LR Duncan, HS Sader, RK Flamm, RE Mendes

JMI Laboratories, North Liberty, Iowa, USA

Leonard R. Duncan, PhD
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: leonard-duncan@jmilabs.com

INTRODUCTION

- Telavancin is a once-daily parenteral bactericidal lipoglycopeptide antimicrobial agent[1]
- Telavancin exhibits a dual mechanism of action that involves inhibition of peptidoglycan synthesis and disruption of bacterial cell membrane function[2]
- Telavancin is approved in the United States for the treatment of adult patients with complicated skin and skin structure infections (cSSSIs) and hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) caused by susceptible isolates of *Staphylococcus aureus* when alternative treatments are not suitable[1]
- Telavancin exhibited efficacy comparable to vancomycin in a limited number of patients with either cSSSIs or HABP/VABP and concurrent *S. aureus* bacteremia[1,3]
- This study evaluated the activity of telavancin and comparators against a current collection of *S. aureus* isolates (including multidrug-resistant [MDR] methicillin-resistant *S. aureus* [MRSA]) collected from United States (US) hospitals in 2017

MATERIALS AND METHODS

Bacterial strain collection

- A total of 3,511 *S. aureus* isolates were collected in 2017 from 34 US sites located in all 9 census bureau divisions
- Isolates were principally from cSSSIs (48.0%), pneumonia in hospitalized patients (24.7%), and bloodstream infections (BSIs; 21.7%) (**Figure 1**)

Antimicrobial susceptibility test methods and MDR definition

- Isolates were tested for susceptibility by current Clinical and Laboratory Standards Institute (CLSI) methods, and MIC interpretations used current CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria[4-6]
- Telavancin broth microdilution MIC testing followed the CLSI-approved method, which includes supplementation with 0.002% polysorbate-80[5]
- The MIC medium for daptomycin testing was supplemented to 50 mg/L calcium[5]
- Bacterial inoculum densities were monitored by colony counts
- MIC values were validated by concurrently tested CLSI-recommended quality control reference strains (*S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212)[4]
- An MRSA isolate was considered MDR if it was resistant to ≥3 of the following antimicrobials (using CLSI interpretive criteria[4], where applicable): ceftaroline, clindamycin, daptomycin, erythromycin, gentamicin, levofloxacin, linezolid, teicoplanin, tetracycline, trimethoprim-sulfamethoxazole, and vancomycin

RESULTS

- Telavancin inhibited all *S. aureus* isolates at ≤0.12 µg/mL (the susceptibility breakpoint), with identical $MIC_{50/90}$ values (0.06/0.06 µg/mL; **Table 1**) observed in all 9 US census divisions
- Equivalent MIC values ($MIC_{50/90}$, 0.06/0.06 µg/mL) were obtained for methicillin-susceptible *S. aureus* (MSSA), MRSA, and MDR MRSA isolates (**Table 1**)
- The prevalence of MRSA (32.8-61.7%) and MDR MRSA (16.6-35.2%) varied by US census division (**Figure 2**)
- Isolates with elevated vancomycin MIC values (2 µg/mL) remained susceptible to telavancin ($MIC_{50/90}$, 0.06/0.12 µg/mL; **Table 1** and **Figure 3**)
- Among tested antimicrobials available for use in the United States, only telavancin ($MIC_{50/90}$, 0.06/0.06 µg/mL; 100.0% susceptible), daptomycin ($MIC_{50/90}$, 0.25/0.25 µg/mL; 99.8% susceptible), linezolid ($MIC_{50/90}$, 1/2 µg/mL; 100.0% susceptible), trimethoprim-sulfamethoxazole ($MIC_{50/90}$, ≤0.5/1 µg/mL; 91.1% susceptible), and vancomycin ($MIC_{50/90}$, 1/1 µg/mL; 100.0% susceptible) exhibited good activity against the MDR MRSA isolate subset. Based on MIC values, telavancin was 4- to 32-fold more potent than these comparators (**Table 2**)
- Ceftaroline ($MIC_{50/90}$, 1/2 µg/mL; 81.6% susceptible) exhibited lower activity against the MDR MRSA isolate subset (**Table 2**)

Table 1. MIC distributions for telavancin tested against 3,511 *S. aureus* isolates from the United States (2017)

Organism/organism group (no. of isolates)	No. of isolates at MIC (cumulative %), µg/mL					MIC_{50}	MIC_{90}
	≤0.008	0.015	0.03	0.06	0.12		
Staphylococcus aureus (3,511)	0 (0.0)	11 (0.3)	1,333 (38.3)	2,142 (99.3)	25 (100.0)	0.06	0.06
MSSA (1,994)	0 (0.0)	6 (0.3)	787 (39.8)	1,190 (99.4)	11 (100.0)	0.06	0.06
MRSA (1,517)	0 (0.0)	5 (0.3)	546 (36.3)	952 (99.1)	14 (100.0)	0.06	0.06
MDR MRSA (414)	0 (0.0)	2 (0.5)	131 (32.1)	277 (99.0)	4 (100.0)	0.06	0.06
Vancomycin (MIC, <2 µg/mL) (3,470)	0 (0.0)	11 (0.3)	1,331 (38.7)	2,111 (99.5)	17 (100.0)	0.06	0.06
Vancomycin (MIC, 2 µg/mL) (41)	–	0 (0.0)	2 (4.9)	31 (80.5)	8 (100.0)	0.06	0.12

MDR, multidrug-resistant; MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

Table 2. Antimicrobial activity for telavancin and comparator agents tested against 414 MDR MRSA isolates from the United States (2017)

Antimicrobial agent	MIC value (µg/mL)			CLSI[a]			EUCAST[a]		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R	%S	%I	%R
Telavancin	0.06	0.06	0.015 to 0.12	100.0	–	–	100.0	–	0.0[b]
Ceftaroline	1	2	0.25 to 2	81.6	18.4	0.0	81.6	18.4	0.0[c]
Clindamycin	>2	>2	≤0.03 to >2	11.6	0.0	88.4	11.4	0.2	88.4
Daptomycin	0.25	0.25	≤0.12 to 2	99.8	–	–	99.8	–	0.2
Erythromycin	>8	>8	0.12 to >8	0.2	0.0	99.8	0.2	0.0	99.8
Gentamicin	≤1	>8	≤1 to >8	89.1	0.0	10.9	88.9	–	11.1
Levofloxacin	>4	>4	0.25 to >4	1.7	0.0	98.3	1.7	–	98.3
Linezolid	1	2	0.25 to 4	100.0	–	0.0	100.0	–	0.0
Teicoplanin	0.5	0.5	≤0.12 to 4	100.0	0.0	0.0	99.8	–	0.2
Tetracycline	≤0.5	>8	≤0.5 to >8	82.9	0.2	16.9	76.8	5.3	17.9
Trimethoprim-sulfamethoxazole	≤0.5	1	≤0.5 to >16	91.1	–	8.9	91.1	0.2	8.7
Vancomycin	1	1	0.5 to 2	100.0	0.0	0.0	100.0	–	0.0

CLSI, Clinical and Laboratory Standards Institute; European Committee on Antimicrobial Susceptibility Testing (EUCAST); I, intermediate; MDR, multidrug-resistant; MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; R, resistant; S, susceptible.
[a]Criteria as published by CLSI 2018 and EUCAST 2018.
[b]Breakpoint applied to all *S. aureus* but approved for MRSA isolates only.
[c]Using other than pneumonia breakpoints.

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

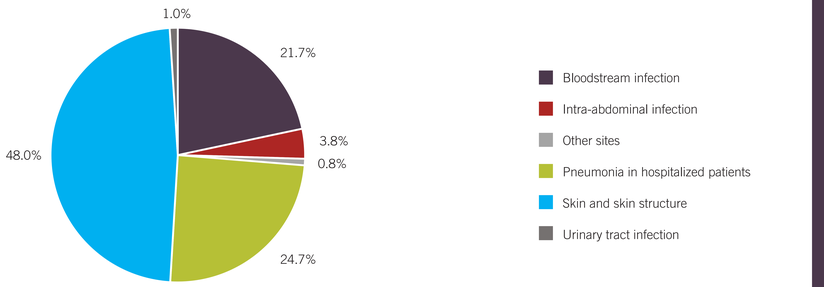
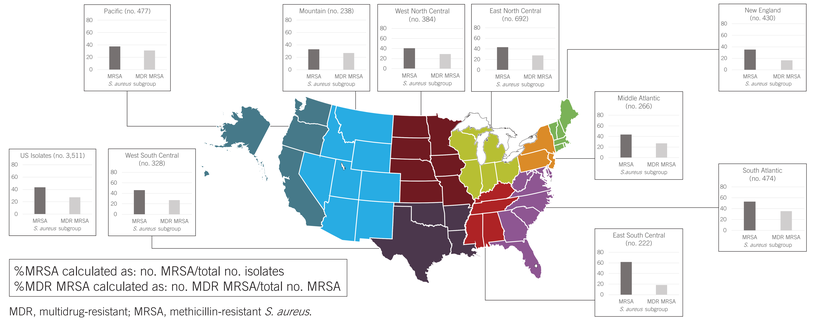


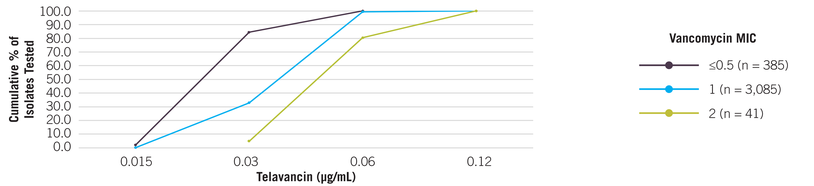
Figure 2. Prevalence of MRSA and MDR MRSA isolates by US Census Bureau division



%MRSA calculated as: no. MRSA/total no. isolates
%MDR MRSA calculated as: no. MDR MRSA/total no. MRSA

MDR, multidrug-resistant; MRSA, methicillin-resistant *S. aureus*.

Figure 3. Telavancin activity against all *S. aureus* US isolates stratified by vancomycin MIC (2017)



MIC, minimal inhibitory concentration.

CONCLUSIONS

- Telavancin exhibited potent *in vitro* antimicrobial activity against a current US collection of *S. aureus* clinical isolates from 2017, including MDR MRSA
- The potency of telavancin was 4- to 32-fold greater than tested comparators
- These data indicate that telavancin has potent *in vitro* activity against *S. aureus* isolated from cSSSIs, pneumonia, and bloodstream infections, regardless of the resistance phenotype

ACKNOWLEDGEMENTS

The research and publication process was supported by Theravance Biopharma R&D, Inc. Poster production support was coordinated by AlphaBioCom and funded by Theravance Biopharma US, Inc.

REFERENCES

1) VIBATIV® (telavancin), USP [package insert]. South San Francisco, CA: Theravance Biopharma US, Inc.; 2016; **2)** Higgins LD, Chang R, Debabov DV, et al. *Antimicrob Agents Chemother.* (2005) 49:1127-1134; **3)** Corey GR, Rubinstein E, Stryjewski ME, et al. *Clin Infect Dis.* (2015) 60:787-796; **4)** Clinical and Laboratory Standards Institute (2018). *M100Ed28E. Performance standards for antimicrobial susceptibility testing: 28th informational supplement.* Wayne, PA: CLSI; **5)** Clinical and Laboratory Standards Institute (2018). *M07Ed11E. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard - eleventh edition.* Wayne, PA: CLSI; **6)** EUCAST (2018). Breakpoint tables for interpretation of MICs and zone diameters. Version 8.0, January 2018. Available at: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_8.0_Breakpoint_Tables.pdf. Accessed January 2018.