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Antimicrobial Activity of Dalbavancin Tested against *Staphylococcus aureus* with Decreased Susceptibility to Glycopeptides, Daptomycin, and/or Linezolid from United States Medical Centers

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INTRODUCTION

- Dalbavancin was approved in the United States (2014) and Europe (2015) to treat adults with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group, and vancomycin-susceptible *Enterococcus faecalis*
- Dalbavancin allows for very convenient parenteral administration to treat ABSSSI, which can be a single dose of 1500 mg or a dose of 1000 mg followed by 500 mg a week later
- Vancomycin, linezolid, daptomycin, telavancin, and teicoplanin are very active against staphylococci, but isolates with decreased susceptibility to these antimicrobial agents are isolated sporadically
- Dalbavancin activity was assessed against a large collection of *S. aureus* clinical isolates with decreased susceptibility to these key antimicrobial agents used to treat severe *S. aureus* infections

MATERIALS AND METHODS

Bacterial isolates

- The organism collection evaluated in this investigation included:
  - Isolates with decreased susceptibility to vancomycin (MIC ≥2 µg/mL): 1,141 isolates
  - Isolates nonsusceptible to daptomycin (MIC ≥2 µg/mL): 48 isolates
  - Isolates with decreased susceptibility to telavancin (MIC ≥0.12 µg/mL): 52 isolates
  - Isolates with decreased susceptibility to teicoplanin (MIC ≥4 µg/mL): 143 isolates
  - Isolates resistant to linezolid (MIC ≥8 µg/mL): 25 isolates
- Isolates were selected from among 59,903 isolates collected from 139 US medical centers between 2002 and 2016 (telavancin was tested only against isolates collected in the 2011–2016 period)
- Isolates were determined to be clinically significant based on local guidelines and were submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA)
- Isolates were initially identified by the participating laboratory, and bacterial identifications were confirmed by the reference monitoring laboratory when necessary

Antimicrobial susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following guidelines in the CLSI M07–A10 document, and testing was performed using reference 96-well panels manufactured by JMI Laboratories
- Quality assurance was performed by concurrently testing CLSI–recommended QC reference strains (*S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, and *Streptococcus pneumoniae* ATCC 49619), and all QC results were within published acceptable ranges
- Dalbavancin breakpoints approved by the Food and Drug Administration (FDA) for indicated species were applied (ie, ≤0.25 µg/mL), and breakpoint criteria for comparator agents were those from CLSI (M100-S27)

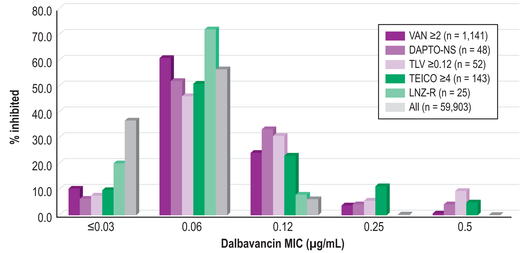
RESULTS

- Only 8 of 59,903 (0.01%) *S. aureus* isolates tested were categorized as dalbavancin-nonsusceptible (MIC, >0.25 µg/mL), all with a dalbavancin MIC of 0.5 µg/mL (Table 1 and Figures 1 and 2) and vancomycin MIC values of 2–4 µg/mL (data not shown)
- Dalbavancin retained activity against 99.3% of isolates with vancomycin MICs of ≥2 µg/mL (Tables 1 and 2), and it was 8-fold more potent than daptomycin against these organisms (Table 2 and Figure 2)
- Daptomycin ($MIC_{50/90}$, 0.5/1 µg/mL) and linezolid ($MIC_{50/90}$, 1/2 µg/mL) were active against 96.8% and 99.6% of isolates, respectively, with decreased susceptibility to vancomycin (Table 2)
- Dalbavancin ($MIC_{50/90}$, 0.06/0.12 µg/mL) and vancomycin ($MIC_{50/90}$, 2/2 µg/mL) retained activity against 95.8% of daptomycin-nonsusceptible *S. aureus* (Table 2)
- When tested against *S. aureus* isolates with teicoplanin MICs of ≥4 µg/mL (nonsusceptible per EUCAST criteria), susceptibility rates for dalbavancin, daptomycin, vancomycin, and linezolid were 95.1%, 95.8%, 97.9%, and 100.0%, respectively; and dalbavancin was 4- to 64-fold more potent than these comparator agents (Table 2)
- All linezolid-resistant isolates (100.0%) were susceptible to dalbavancin ($MIC_{50/90}$, 0.06/0.06 µg/mL), daptomycin ($MIC_{50/90}$, 0.5/0.5 µg/mL), and vancomycin ($MIC_{50/90}$, 1/2 µg/mL), but dalbavancin was 8- and 16- to 32-fold more potent than daptomycin and vancomycin, respectively
- MRSA rates ranged from 71.2%–96.0% among these resistant subsets

CONCLUSIONS

- Dalbavancin retained potent *in vitro* activity against *S. aureus* isolates displaying decreased susceptibility to agents commonly used to treat serious infections and was consistently more potent than comparator agents
- This *in vitro* characteristic along with prolonged half-life and convenient administration make dalbavancin a valuable option for treating *S. aureus* infections, including those caused by multidrug-resistant organisms

Figure 1. Summary of dalbavancin activity when tested against *S. aureus* isolates with decreased susceptibility to glycopeptides, daptomycin, and/or linezolid from United States medical centers



Abbreviations: VAN ≥2, isolates with vancomycin MICs of ≥2 µg/mL; DAPTO-NS, daptomycin-nonsusceptible (MIC, ≥2 µg/mL); TLV ≥0.12 µg/mL, isolates with telavancin MICs of ≥0.12 µg/mL; TEICO ≥4, isolates with teicoplanin MICs of ≥4 µg/mL; LNZ-R, linezolid-resistant

Figure 2. Antimicrobial activity of dalbavancin and daptomycin tested against *S. aureus* isolates with decreased susceptibility to vancomycin (n = 1,141)

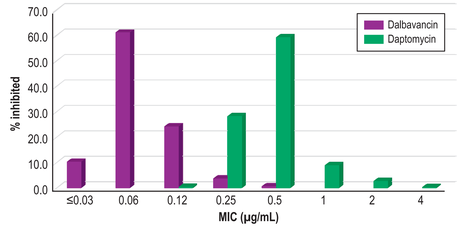


Table 1. Summary of dalbavancin activity when tested against *S. aureus* isolates with decreased susceptibility to glycopeptides, daptomycin, and/or linezolid from United States medical centers

Resistance phenotype (no. tested)	Number of isolates (cumulative %) inhibited at dalbavancin MIC (µg/mL) of:					MIC_{50}	MIC_{90}
	≤0.03	0.06	0.12	0.25	0.5		
Vancomycin MIC ≥2 µg/mL (1,141)	117 (10.3%)	**697 (71.3%)**	276 (95.5%)	43 (99.3%)	8 (100.0%)	0.06	0.12
Daptomycin-nonsusceptible (48)	3 (6.3%)	**25 (58.3%)**	16 (91.7%)	2 (95.8%)	2 (100.0%)	0.06	0.12
Telavancin MIC ≥0.12 µg/mL (52)	4 (7.7%)	**24 (53.8%)**	16 (84.6%)	3 (90.4%)	5 (100.0%)	0.06	0.25
Teicoplanin MIC ≥4 µg/mL (143)	14 (9.8%)	**73 (60.8%)**	33 (83.9%)	16 (95.1%)	7 (100.0%)	0.06	0.25
Linezolid-resistant (25)	5 (20.0%)	**18 (92.0%)**	2 (100.0%)			0.06	0.06
All isolates (59,903)	22,066 (36.8%)	**33,879 (93.4%)**	3,795 (99.7%)	155 (>99.9%)	8 (100.0%)	0.06	0.06

Bold data represent dalbavancin modal MIC results

Table 2. Activity of dalbavancin and comparator antimicrobial agents tested against *S. aureus* isolates with decreased susceptibility to glycopeptides, daptomycin, and/or linezolid from United States medical centers

Organism subset/ antimicrobial agent (n)	MIC_{50}	MIC_{90}	Range	CLSI[a] %S	CLSI[a] %R
Vancomycin MIC ≥2 µg/mL (1,141)					
Dalbavancin	0.06	0.12	≤0.03 to 0.5	99.3[b]	
Daptomycin	0.5	1	≤0.12 to 4	96.8	
Vancomycin	2	2	2 to 4	99.3	0.0
Teicoplanin	≤2	≤2	≤2 to 16	99.9	0.0
Linezolid	1	2	≤0.12 to >8	99.6	0.4
Oxacillin	>2	>2	≤0.25 to >2	26.9	73.1
Daptomycin-nonsusceptible (48)					
Dalbavancin	0.06	0.12	≤0.03 to 0.5	95.8[b]	
Daptomycin	2	4	2 to 4	0.0	
Vancomycin	2	2	1 to 4	95.8	0.0
Teicoplanin	≤2	4	≤2 to 16	97.9	0.0
Linezolid	1	2	0.5 to 4	100.0	0.0
Oxacillin	>2	>2	≤0.25 to >2	12.5	87.5
Telavancin MIC ≥0.12 µg/mL (52)					
Dalbavancin	0.06	0.25	≤0.03 to 0.5	90.4[b]	
Daptomycin	0.5	1	0.25 to 2	96.2	
Vancomycin	1	2	1 to 4	98.1	0.0
Telavancin	0.12	0.12	0.12 to 0.25	96.2	
Teicoplanin	≤2	4	≤2 to 16	98.1	0.0
Linezolid	1	1	0.25 to 2	100.0	0.0
Oxacillin	>2	>2	≤0.25 to >2	34.6	65.4

Table 2. Activity of dalbavancin and comparator antimicrobial agents tested against *S. aureus* isolates with decreased susceptibility to glycopeptides, daptomycin, and/or linezolid from United States medical centers *(continued)*

Organism subset/ antimicrobial agent (n)	MIC_{50}	MIC_{90}	Range	CLSI[a] %S	CLSI[a] %R
Teicoplanin MIC ≥4 µg/mL (143)					
Dalbavancin	0.06	0.25	≤0.03 to 0.5	95.1[b]	
Daptomycin	0.5	1	0.12 to 4	95.8	
Vancomycin	2	2	0.5 to 4	97.9	0.0
Teicoplanin	4	8	4 to 16	99.3	0.0
Linezolid	1	2	0.25 to 4	100.0	0.0
Oxacillin	>2	>2	≤0.25 to >2	26.6	73.4
Linezolid-resistant (25)					
Dalbavancin	0.06	0.06	≤0.03 to 0.12	100.0[b]	
Daptomycin	0.5	0.5	0.25 to 0.5	100.0	
Vancomycin	1	2	0.5 to 2	100.0	0.0
Teicoplanin	≤2	≤2	≤2	100.0	0.0
Linezolid	8	>8	8 to >8	0.0	100.0
Oxacillin	>2	>2	≤0.25 to >2	4.0	96.0

[a] Criteria as published by CLSI [2017] and EUCAST [2017]
[b] Breakpoints from FDA Package Insert

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