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Antimicrobial Susceptibility of Gram-Positive Bacteria Isolated from Patients Hospitalized with Bacteremia in United States and European Medical Centers: Results from the International Dalbavancin Evaluation of Activity (IDEA) Program

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CONCLUSIONS

treatment of BSI

United States and Europe combined

^a Greater than the highest concentration tested.

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INTRODUCTION

- Bloodstream infections (BSIs) are a major cause of morbidity and mortality worldwide
- The etiology of BSIs may vary significantly according to the type of patient and source of
- Dalbavancin belongs to the lipoglycopeptide class of antimicrobial agents that act by interrupting bacterial cell wall synthesis resulting in bacterial death, and it was approved in the United States (USA; 2014) and Europe (EUR; 2015) to treat adults with acute bacterial skin and skin structure infections (ABSSSIs) caused by susceptible isolates of Staphylococcus aureus, including methicillin-resistant (MRSA) and -susceptible S. aureus (MSSA), Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus group, and vancomycin-susceptible Enterococcus faecalis
- Dalbavancin allows for convenient parenteral administration, which can be a single dose of 1500 mg or a dose of 1000 mg followed by 500 mg a week later for treating ABSSSI
- Dalbavancin is not licensed for treating BSI, but is potentially important in treating infections due to highly resistant gram-positive cocci (GPC)
- We evaluated dalbavancin in vitro activity and potency when tested against a large collection of GPC isolates collected from patients with BSIs

MATERIALS AND METHODS

Bacterial isolates

A. United States

β-hemolytic streptococci

- A total of 8,296 unique GPC were consecutively collected from 33 United States (n=4,409) and 39 European (n=3,887) medical centers in 2015–2017 by the International Dalbavancin Evaluation of Activity (IDEA) Program
- 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)
- Participating laboratories initially identified isolates and JMI confirmed bacterial identifications by standard algorithms supported by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany)

S. pneumoniae (4.0%)

Antimicrobial susceptibility testing

Viridans group streptococci -

E. faecalis —

Coagulase-negative staphylococci

E. faecium —

• Isolates were tested for susceptibility (S) by broth microdilution following guidelines in the Clinical and Laboratory Standards Institute (CLSI) M07 document (2018)

Figure 1 Frequency of gram-positive bacteria isolated from patients with BSIs (SENTRY Program, 2015–2017)

S. aureus

Other *Enterococcus* spp. (0.5%)

- CLSI (2018)-approved dalbavancin breakpoints (≤0.25 mg/L) and breakpoint criteria for comparator agents for indicated species were applied
- Quality assurance was performed by concurrently testing CLSI-recommended quality control reference strains (S. aureus ATCC 29213, E. faecalis ATCC 29212, and Streptococcus pneumoniae ATCC 49619)

RESULTS

- The most common organisms were S. aureus (48.3% in USA, 44.3% in EUR), coagulasenegative staphylococci (CoNS; 14.3% in USA, 15.6% in EUR), and *E. faecalis* (11.5% in USA, 13.1% in EUR; Figure 1)
- All *S. aureus* isolates were susceptible to dalbavancin (MIC_{50/00}, 0.03/0.03 mg/L), linezolid (MIC_{50/90}, 1/2 mg/L), vancomycin (MIC_{50/90}, 1/1 mg/L), and teicoplanin (MIC_{50/90}, ≤0.5/≤0.5 mg/L); >99.9% were susceptible to daptomycin (MIC_{50/90}, 0.25/0.5 mg/L; Tables 1 and 2)
- Based on MIC₅₀, dalbavancin (MIC_{50/90}, 0.03/0.03 mg/L) was 8-fold more active than daptomycin (MIC_{50/90}, 0.25/0.5 mg/L) and 32-fold more active than vancomycin (MIC_{50/90}, 1/1 mg/L) against *S. aureus*, and dalbavancin activity was not adversely affected by oxacillin resistance (Table 2)
- Among CoNS isolates, 99.9% were inhibited at a dalbavancin MIC of ≤0.25 mg/L (MIC_{50/90}, 0.03/0.06 mg/L; Table 1); susceptibility to daptomycin (MIC_{50/90}, 0.5/0.5 mg/L), linezolid (MIC_{50/90}, 0.5/1 mg/L), vancomycin (MIC_{50/90}, 1/2 mg/L), and teicoplanin (MIC_{50/90}, 2/4 mg/L) were 100.0%, 96.7%, 100.0%, and 98.3%, respectively (Table 2)
- Among E. faecalis isolates, 97.7% were dalbavancin-susceptible (96.4% in USA, 99.0% in EUR; MIC_{50/90}, 0.03/0.06 mg/L), 97.5% were vancomycin-susceptible (96.1% in USA, 99.0% in EUR; MIC_{50/90}, 1/2 mg/L), and all isolates were susceptible to ampicillin (MIC_{50/90}, 1/1 mg/L), daptomycin (MIC_{50/90}, 0.5/1 mg/L), and linezolid (MIC_{50/90}, 1/2 mg/L; Table 2)

Other *Enterococcus* spp. (0.6%)

S. aureus

 Among E. faecium isolates (n=656; 7.9% overall), 63.9% were inhibited at ≤0.25 mg/L of dalbavancin (33.4% in USA, 87.5% in EUR) and 61.6% were vancomycin-susceptible (32.8% in USA, 84.0% in EUR; Tables 1 and 2)

S. pneumoniae —

Table 1 Antimicrobial activity of dalbavancin tested against the main organisms and organism groups from

No. and cumulative % of isolates inhibited at MIC (mg/L) of:

enterococci, BHS, and VGS isolated from patients with BSIs

daptomycin and vancomycin against these organisms

overall]; MIC_{50/90}, 0.015/0.03 mg/L; Tables 1 and 2)

Dalbavancin was highly active against β-hemolytic streptococci (BHS; n=686 [8.3%]

Dalbavancin was very active against S. aureus, CoNS, vancomycin-susceptible

Based on MIC₅₀ values, dalbavancin was generally 8- to 32-fold more active than

• These results support further investigations to determine the role of dalbavancin in the

overall]; MIC_{50/90}, 0.015/0.03 mg/L) and viridans group streptococci (VGS; n=432 [5.2%

group (no. of solates)	≤0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	> a	MIC ₅₀	MIC ₉₀
Staphylococcus	0	4	24	418	3,060	332	12	2					0.00	0.00
aureus (3,852)	0.0	0.1	0.7	11.6	91.0	99.6	99.9	100.0					0.03	0.03
Coagulase-negative	1	8	34	280	655	200	53	3				1	0.00	0.00
staphylococci (1,235)	0.1	0.7	3.5	26.2	79.2	95.4	99.7	99.9				100.0	0.03	0.06
Staphylococcus	0	2	8	153	473	110	8	0				1	0.02	0.06
epidermidis (755)	0.0	0.3	1.3	21.6	84.2	98.8	99.9	99.9				100.0	0.03	0.06
Staphylococcus		0	1	2	18	46	40	3					0.06	0.12
haemolyticus (110)		0.0	0.9	2.7	19.1	60.9	97.3	100.0					0.06	0.12
Staphylococcus		0	1	66	98	16	1						0.03	0.03
hominis (182)		0.0	0.5	36.8	90.7	99.5	100.0						0.03	0.03
Enterococcus spp.				166	790	374	109	21	1	3	12	244	0.03	>2
(1,720)				9.7	55.6	77.3	83.7	84.9	84.9	85.1	85.8	100.0	0.03	
Enterococcus				118	667	197	11	2	0	0	1	22	0.03	0.06
faecalis (1,018)				11.6	77.1	96.5	97.5	97.7	97.7	97.7	97.8	100.0	0.00	0.00
Enterococcus				42	109	166	85	17	1	3	11	222	0.12	>2
faecium (656)				6.4	23.0	48.3	61.3	63.9	64.0	64.5	66.2	100.0	0.12	
Other Enterococcus				6	14	11	13	2					0.06	0.12
spp. (46)				13.0	43.5	67.4	95.7	100.0					0.00	0.12
3-hemolytic		121	207	257	75	24	2						0.015	0.03
streptococci (686)		17.6	47.8	85.3	96.2	99.7	100.0						0.010	0.00
Streptococcus		5	59	180	42	12							0.015	0.03
agalactiae (298)		1.7	21.5	81.9	96.0	100.0							01010	0100
Streptococcus		15	59	43	24	10	2						0.015	0.03
dysgalactiae (153)		9.8	48.4	76.5	92.2	98.7	100.0						01010	0.00
Streptococcus		101	89	34	9	2							0.008	0.015
pyogenes (235)		43.0	80.9	95.3	99.1	100.0	0							
/iridans group		82	91	111	116	24	8						0.015	0.03
streptococci (432)		19.0	40.0	65.7	92.6	98.1	100.0							
Streptococcus (CA)		59	5										≤0.004	≤0.004
anginosus group (64)		92.2	100.0	10	07									
Streptococcus bovis		6	10	19 56.5	27								0.015	0.03
group (62)		9.7	25.8	56.5	100.0		6							
Streptococcus mitis		14	60	75 60.9	75	15	6						0.015	0.03
group (245)		5.7	30.2	60.8	91.4	97.6	100.0							
Streptococcus			0	14.0	5 95.7	100.0							0.03	
mutans group (7)		2	0.0	14.3 16	85.7 9	100.0	2							
Streptococcus		3	16				_						0.015	0.06
Stroptococus		5.6 5	35.2	64.8	81.5 23	96.3	100.0							
Streptococcus			103	240									0.015	0.015
oneumoniae (371)		1.3	29.1	93.8	100.0									

Table 2 Antimicrobial activity of dalbavancin and comparator agents tested against 8,296 gram-positive cocci isolated from patients with BSIs in the United States (USA, n=4,409) and Europe (EUR; n=3,887)

Organism/			US		EUR		
antimicrobial agent	MIC ₅₀ a	MIC ₉₀ a	0/ 0-	0/ 🗖 -	0/ 00	0/ -	
(no. tested in USA/	50	90	%S ^a	%R ^a	%S ^a	%R ^a	
EUR)							
<i>S. aureus</i> (2,130/1,722)		0.00	4000		400.0		
Dalbavancin	0.03	0.03	100.0		100.0		
Teicoplanin	≤0.5	≤0.5	100.0	0.0	100.0	0.0	
Vancomycin	1	1	100.0	0.0	100.0	0.0	
Daptomycin	0.25	0.5	>99.9		100.0		
Linezolid	1	2	100.0	0.0	100.0	0.0	
Oxacillin	0.5	>2	58.4	41.6	74.8	25.2	
Clindamycin	≤0.25	>2	85.1	14.6	93.6	6.4	
Levofloxacin	0.25	>4	62.2	37.0	76.2	23.4	
Tetracycline	≤0.5	≤0.5	96.2	3.1	94.3	5.0	
TMP-SMX ^b	≤0.5	≤0.5	97.6	2.4	99.2	8.0	
CoNS (629/606)					<u> </u>		
Dalbavancin	0.03	0.06	(100.0) ^c		(100.0) ^c		
Teicoplanin	2	4	98.3	0.0	98.8	0.0	
Vancomycin	1	2	100.0	0.0	100.0	0.0	
Daptomycin	0.5	0.5	100.0		99.8		
Linezolid	0.5	1	96.7	3.3	98.5	1.5	
Oxacillin	>2	>2	34.3	65.7	28.9	71.1	
Clindamycin	≤0.25	>2	65.2	33.4	71.1	26.6	
Levofloxacin	2	>4	50.9	47.4	42.4	52.1	
Tetracycline	≤0.5	>8	83.3	15.9	88.1	9.7	
TMP-SMX	≤0.5	>4	65.3	34.7	63.7	36.3	
E. faecalis (507/511)		<u>I</u>					
Dalbavancin	0.03	0.06	96.4 ^d		99.0 ^d		
Teicoplanin	≤2	≤2	96.4	3.6	99.0	1.0	
Vancomycin	1	2	96.1	3.9	99.0	1.0	
Daptomycin	0.5	1	100.0		100.0		
Linezolid	1	2	100.0	0.0	100.0	0.0	
Ampicillin	1	1	100.0	0.0	100.0	0.0	
Levofloxacin	1	>4	75.3	24.7	68.9	29.9	
E. faecium (287/369)	· ·	•					
Dalbavancin	>2	>2	(33.4) ^d		(87.5) ^d		
Teicoplanin	≤2	>16	34.5	58.9	87.5	10.3	
Vancomycin	_ <u></u> 1	>16	32.8	67.2	84.0	14.9	
Daptomycin	1	2	98.6	01.2	100.0	17.0	
Linezolid	1	2	99.0	0.7	98.9	0.5	
Ampicillin	>8	>8	18.8	81.2	9.2	90.8	
Levofloxacin	>4	>4	11.1	82.2	4.9	91.9	

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Organism/			US	SA	EUR		
antimicrobial agent (no. tested in USA/ EUR)	MIC ₅₀ ^a	MIC ₉₀ ^a	%S ^a	%R ^a	%S ^a	%Rª	
β-hemolytic streptocod	cci (420/266)						
Dalbavancin	0.015	0.03	100.0e		100.0e		
Vancomycin	0.5	0.5	100.0		100.0		
Daptomycin	0.12	0.25	100.0		100.0		
Linezolid	1	2	100.0		100.0		
Ceftriaxone	≤0.03	0.06	100.0		100.0		
Penicillin	≤0.03	0.06	100.0		100.0		
Clindamycin	≤0.25	>2	81.7	17.6	90.6	9.0	
Levofloxacin	0.5	1	99.3	0.2	98.5	1.5	
Tetracycline	1	>4	48.8	49.3	56.0	43.2	
Viridans group strepto	cocci (235/19	7)					
Dalbavancin	0.015	0.03	100.0e		100.0e		
Vancomycin	0.5	0.5	100.0		100.0		
Daptomycin	0.25	0.5	100.0		100.0		
Linezolid	1	1	100.0		100.0		
Ceftriaxone	0.12	1	93.2	4.7	96.4	1.5	
Penicillin	0.06	1	67.7	5.1	78.2	1.5	
Clindamycin	≤0.25	>2	86.4	12.8	91.9	8.1	
Levofloxacin	1	>4	87.7	11.5	97.0	1.5	
Tetracycline	1	>4	61.3	35.3	70.1	27.9	
S. pneumoniae (177/19	94)						
Dalbavancin	0.015	0.015	100.0e		100.0e		
Vancomycin	0.25	0.5	100.0		100.0		
Linezolid	1	2	100.0		100.0		
	0.03	0.5	92.7 ^f	1.1 ^f	91.2 ^f	4.1 ^f	
Ceftriaxone			98.9 ^g	0.0g	95.9 ^g	1.5 ⁹	
	≤0.06	1	75.1 ^h	6.2 ^h	83.5 ^h	8.2 ^h	
Penicillin			98.3 ⁱ	0.0^{i}	94.8 ⁱ	0.0^{i}	
Clindamycin	≤0.25	≤0.25	90.3	9.1	87.1	12.9	
Erythromycin	0.03	>2	64.4	33.9	82.5	17.0	
Levofloxacin	1	1	100.0	0.0	99.0	1.0	
Tetracycline	≤0.25	>4	85.9	14.1	83.0	17.0	
TMP-SMX	≤0.5	2	82.5	6.8	77.3	14.9	

- ^a MIC₅₀ and MIC₉₀ values for the US and EUR collection combined; criteria as published by CLSI 2018. ^b TMP-SMX, trimethoprim-sulfamethoxazole.
- akpoint applied to all *E. faecalis* and *E. faecium* isolates, but approved for vancomycin-susceptible *E. faecalis* isolates only. Breakpoint applied to all Streptococcus spp., but approved for S. pyogenes, S. agalactiae, S. dysgalactiae, and S. anginosus group only.
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E. faecalis —

Coagulase-negative staphylococci -

β-hemolytic streptococci —

Viridans group streptococci -

E. faecium —

B. Europe