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ANTIMICROBIAL SUSCEPTIBILITY OF ENTEROCOCCI AND STREPTOCOCCI FROM UNITED STATES HOSPITALS: A 9-YEAR SUMMARY OF THE DAPTOMYCIN SURVEILLANCE PROGRAM (2002-2010)

H.S. Sader, P.R. Rhomberg, D.J. Farrell, R.N. Jones

JMI Laboratories, North Liberty, IA, USA

HELIO S. SADER, M.D., PH.D.
JMI LABORATORIES
345 BEAVER KREEK CENTRE, SUITE A
NORTH LIBERTY IA 52317 USA
PHONE: (319) 665-3370
E-MAIL: HELIO-SADER@JMILABS.COM

ABSTRACT

Objectives: To evaluate the activities of daptomycin (DAP) and comparator agents tested against enterococci and streptococci (beta-haemolytic [BHS] and viridans group [VGS]) collected from USA hospitals in 2002-2010. DAP was first approved by the USA-FDA in 2003 and by the European Medicines Agency (EMEA) in 2005; and has increasingly been used to treat bacteremia and acute bacterial skin and skin structure infections (ABSSSI) worldwide.

Methods: Unique patient strains of clinical significance were consecutively collected in 67 USA medical centers and susceptibility (S) tested in a central reference laboratory against DAP and various comparators by CLSI broth microdilution methods. Mueller-Hinton broth was supplemented to 50 mg/L of calcium when testing DAP.

Results: 14,044 strains were evaluated, including 5,977 *E. faecalis* (EF; 95.2% vancomycin [VAN]-S), 3,735 *E. faecium* (EFM; 79.6% VAN-R), 3,246 BHS and 1,086 VGS. Isolates were mostly from bacteremia (62%), ABSSSI (15%) and urinary tract infections (13%). DAP-S rates were 99.97, 99.60, 100.0 and 99.63% for EF, EFM, BHS and VGS, respectively. VAN resistance (R; MIC, >4 mg/L) increased progressively from 64.9% in 2002 to 79.1% in 2010 among EFM, while VAN-R EF increased from 2.8% in 2002 to 6.4% in 2008, but decreased to 2.9 and 3.3% in 2009 and 2010, respectively. Only 17 DAP-non-S enterococci (0.18%) were observed, 2 EF (0.03%) and 15 EFM (0.40%). Importantly, VAN-S and VAN-non-S enterococci exhibited very similar DAP MIC distributions (**Table 1**). DAP was very active against VAN-non-S EF ($MIC_{50/90}$, 0.5/1 mg/L) and EFM ($MIC_{50/90}$, 2/4 mg/L). Linezolid was also very active against EF ($MIC_{50/90}$, 1/2 mg/L; 99.85% S) and EFM ($MIC_{50/90}$, 1/2 mg/L; 98.5% S). BHS were very S to DAP ($MIC_{50/90}$, ≤0.12/0.25 mg/L; 100.0% S) and most other antimicrobials tested. DAP was also highly active against VGS ($MIC_{50/90}$, 0.25/0.5 mg/L; 99.63% S).

Conclusion: DAP demonstrated sustained activity against an extensive sampling of clinical isolates of enterococci (including >3,000 VAN-R strains) and streptococci from numerous USA medical centres over the last 9 years (99.85% S overall). DAP activity was not adversely influenced by R to other antimicrobial classes, including VAN among enterococci.

INTRODUCTION

Staphylococcus aureus, enterococci and streptococci are important Gram-positive pathogens causing serious infections in the hospital environment. These organisms are often multidrug-resistant (MDR) with limited therapeutic options. Daptomycin is a lipopeptide with rapid *in vitro* bactericidal activity against a wide spectrum of Gram-positive organisms, including MDR strains of staphylococci and enterococci.

Daptomycin was approved by the United States (USA) Food and Drug Administration (USA-FDA) in 2003 and by the European Medicines Agency (EMEA) in 2005 for the treatment of acute bacterial skin and skin structure infections (ABSSSI) using a dose of 4 mg/kg every 24 hours and for treatment of *S. aureus* bacteremia and right-sided endocarditis at a dose of 6 mg/kg every 24 hours.

As part of the Daptomycin ACTIV™ Surveillance Program, we evaluated daptomycin activity trends against enterococci and streptococci over a 9-year period (2002-2010).

MATERIALS AND METHODS

Bacterial Isolates: In the Daptomycin ACTIV™ Surveillance Program, consecutive unique patient strains of clinical significance were collected between January 2002 and December 2010 in 67 USA medical centers. The isolates were collected largely from bloodstream infections (62%), ABSSSI (15%) and urinary tract (13%) infections in hospitalized patients according to a common surveillance design. The isolates were identified locally and forwarded to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) for confirmation of species identification, when necessary, and reference antimicrobial susceptibility testing. The collection of organisms tested included: 5,977 *E. faecalis* (4.8% vancomycin non-susceptible); 3,735 *E. faecium* (79.6% vancomycin non-susceptible); 3,246 β-haemolytic streptococci and 1,086 viridans group streptococci.

MATERIALS AND METHODS

Susceptibility test methods: Daptomycin and various comparator agents were tested by Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods in validated, microdilution panels manufactured by TREK Diagnostics Systems (Cleveland, Ohio, USA). The test medium was cation adjusted Mueller-Hinton broth (CA-MHB) adjusted to contain physiological levels of calcium (50 mg/L) when testing daptomycin against enterococci and CA-MHB with 2-5% lysed horse blood when testing streptococci. CLSI and EUCAST interpretive criteria were used to categorize the isolates as susceptible, intermediate and resistant. A daptomycin susceptibility breakpoint of ≤4 mg/L was used for the enterococcal and ≤1 mg/L was used for the streptococcal results, as recommended by the CLSI and the USA-FDA. EUCAST has established daptomycin susceptible and resistant breakpoints for β-haemolytic streptococci (≤1 and >1 mg/L, respectively), but has not published daptomycin breakpoints for enterococcal or viridans group streptococcal strains. The following quality control organisms were concurrently tested: *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619.

RESULTS

- Daptomycin was very active against the 5,977 *E. faecalis* (99.97% susceptible) and 3,735 *E. faecium* (99.60% susceptible) strains collected from USA medical centers (**Table 1**). Overall vancomycin resistance rates (CLSI/EUCAST) were 4.4/4.8% for *E. faecalis* and 79.4/79.6% for *E. faecium* (**Table 2**).
- The *E. faecalis* and *E. faecium* daptomycin MIC distributions were nearly identical when comparing vancomycin-susceptible ($MIC_{50/90}$, 1/1 and 2/4 mg/L) and vancomycin-non-susceptible ($MIC_{50/90}$, 0.5/1 and 2/4 mg/L) organism subset populations, respectively (**Table 1**).
- Daptomycin was two- to four-fold more active against *E. faecalis* ($MIC_{50/90}$, 0.5-1/1 mg/L) compared to *E. faecium* ($MIC_{50/90}$, 2/4 mg/L; **Table 2**)
- Only 17 daptomycin non-susceptible enterococci (0.18%) were observed, among both *E. faecalis* (2; 0.03%) and *E. faecium* (15; 0.40%) strains with no increasing trend over the study period (**Tables 1 and 3**).
- When analyzed over time, daptomycin showed stable susceptibility rates (range 98.7 - 100.0%) between 2002 and 2010. In contrast, vancomycin showed a constant trend toward increasing resistance among *E. faecium* (from 64.9 to 79.1%). Among *E. faecalis*, vancomycin resistance increased from 2.8 in 2002 to 6.4% in 2008, but decreased to 2.9 and 3.3% in 2009 and 2010; **Table 3**).
- Linezolid was very active against both *E faecialis* ($MIC_{50/90}$, 1/2 mg/L; 99.0-99.9% susceptible) and *E. faecium* ($MIC_{50/90}$, 2/4 mg/L; 98.3-99.0% susceptible) strains, and its potency was not affected by vancomycin susceptibility. In contrast, levofloxacin was active against 66.9 and 23.2% of vancomycin-susceptible and only 2.1 and 0.2% of vancomycin-non-susceptible *E. faecalis* and *E. faecium* strains, respectively, at the CLSI susceptible breakpoint (**Table 2**).
- Daptomycin was very active against the 3,246 β-haemolytic streptococci ($MIC_{50/90}$, ≤0.12/0.25 mg/L, 100.0% susceptible) and 1,086 viridans group streptococci ($MIC_{50/90}$, 0.25/0.5 mg/L; 99.63% susceptible) strains collected from USA medical centers.
- All agents tested showed excellent coverage against β-haemolytic streptococci with susceptibility rates at >96% based on CLSI and EUCAST breakpoints. Viridans group streptococci were less susceptible than β-haemolytic streptococci to most agents tested with lowest susceptibility observed to penicillin (73.4%) and levofloxacin (91.8%; **Table 2**).

RESULTS

Table 1. Comparison of *in vitro* activity of daptomycin and selected antimicrobial agents tested against enterococci and streptococci

Organism/phenotype (no. of isolates)	Number of strains (cumulative %) inhibited at daptomycin MIC (mg/L) of: ≤0.12	0.25	0.5	1	2	4	8	no. (%) DAP non-S
E. faecalis (5,977)								
vancomycin-susceptible (5,689)	67 (1.2)	246 (5.5)	2302 (46.0)	2653 (92.6)	400 (99.6)	19 (>99.9)	2 (100.0)	2 (0.04)
vancomycin-non- susceptible (288)	4 (1.4)	20 (8.3)	125 (51.7)	115 (91.7)	24 (100.0)			0 (0.00)
E. faecium (3,735)								
vancomycin- susceptible (762)	9 (1.2)	9 (2.4)	32 (6.6)	187 (31.1)	406 (84.4)	114 (99.3)	4 (99.9)	5 (0.66)
vancomycin-non- susceptible (2,973)	11 (0.4)	22 (1.1)	111 (4.8)	766 (30.6)	1662 (86.5)	391 (99.7)	10 (100.0)	10 (0.34)
β-haemolytic streptococci (3,246)	2383 (73.4)	776 (97.3)	87 (100.0)					0 (0.00)
Viridans group streptococci (1,086)	356 (32.8)	330 (63.2)	300 (90.8)	96 (99.6)	4 (100.0)[a]			4 (0.37)[a]

a. Includes *S. constellatus* (1) and *S. mitis* (3)

Table 2. Antimicrobial activity of daptomycin and comparator agents when tested against bacterial isolates from USA medical centers

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
E. faecalis (5,689)					
Vancomycin-susceptible (5,689)					
Daptomycin	1	1	≤0.12 - 8	>99.9 / -	- / -
Ampicillin	≤2	≤2	≤2 - >16	99.8 / 0.1	99.6 / 0.1
Levofloxacin	1	>4	≤0.5 - >4	66.9 / 32.7	- / -
Linezolid	1	2	≤0.25 - >8	99.9 / 0.1	99.9 / 0.1
Teicoplanin	≤2	≤2	≤2 - 4	100.0 / 0.0	99.9 / 0.1
Vancomycin	1	2	≤0.12 - 4	100.0 / 0.0	100.0 / 0.0
Vancomycin-non-susceptible (288)					
Daptomycin	0.5	1	≤0.12 - 2	100.0 / -	- / -
Ampicillin	≤2	≤2	≤2 - >16	97.6 / 2.4	97.6 / 2.4
Levofloxacin	>4	>4	1 - >4	2.1 / 96.9	- / -
Linezolid	1	2	0.5 - >8	99.0 / 1.0	99.0 / 1.0
Teicoplanin	>8	>8	≤2 - >8	40.6 / 50.7	37.9 / 62.1
Vancomycin	>16	>16	8 - >16	0.0 / 91.3	0.0 / 100.0
E. faecium					
Vancomycin-susceptible (762)					
Daptomycin	2	4	≤0.12 - >8	99.3 / -	- / -
Ampicillin	>16	>16	≤2 - >16	25.5 / 74.5	24.7 / 74.5
Levofloxacin	>4	>4	≤0.5 - >4	23.2 / 70.3	- / -
Linezolid	1	2	≤0.25 - >8	99.0 / 1.0	99.0 / 1.0
Teicoplanin	≤2	≤2	≤2 - 4	100.0 / 0.0	99.5 / 0.0
Vancomycin	1	1	0.25 - 4	100.0 / 0.0	100.0 / 0.0
Vancomycin-non-susceptible (2,973)					
Daptomycin	2	4	≤0.12 - 8	99.7 / -	- / -
Ampicillin	>8	>8	≤2 - >8	0.5 / 99.5	0.4 / 99.5
Levofloxacin	>4	>4	≤0.5 - >4	0.2 / 99.7	- / -
Linezolid	1	2	≤0.25 - >8	98.3 / 1.4	98.6 / 1.4
Teicoplanin	>8	>8	≤2 - >8	5.9 / 85.0	4.2 / 95.8
Vancomycin	>16	>16	8 - >16	0.0 / 99.2	0.0 / 100.0
β-haemolytic streptococci (3,246)					
Daptomycin	≤0.12	0.25	≤0.12 - 0.5	100.0 / -	100.0 / 0.0
Ampicillin	≤2	≤2	≤2 - 4	- / -	100.0 / 0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25 - 2	99.9 / -	100.0 / 0.0
Levofloxacin	≤0.5	1	≤0.5 - >4	99.0 / 0.9	96.2 / 1.1
Linezolid	1	1	≤0.12 - 2	100.0 / -	100.0 / 0.0
Penicillin	≤0.03	0.06	≤0.03 - 0.12	100.0 / -	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2 - 4	- / -	99.9 / 0.1
Vancomycin	0.5	0.5	≤0.12 - 1	100.0 / -	100.0 / 0.0
Viridans Group streptococci (1,086)					
Daptomycin	0.25	0.5	≤0.12 - 2	99.6 / -	- / -
Ceftriaxone	≤0.25	1	≤0.25 - 32	94.0 / 2.8	89.0 / 11.0
Levofloxacin	1	2	≤0.5 - >4	91.8 / 6.9	- / -
Linezolid	1	1	≤0.12 - 2	100.0 / -	- / -
Penicillin	0.06	1	≤0.03 - >4	73.4 / 4.2	81.5 / 4.2
Teicoplanin	≤2	≤2	≤2 - 4	- / -	99.6 / 0.4
Vancomycin	0.5	1	≤0.12 - 2	99.9 / -	100.0 / 0.0

a. Criteria as published by the CLSI [2011] and EUCAST [2011].

Table 3. Nine year trend of antimicrobial susceptibility/resistance rates among enterococcal strains collected from USA medical centers

Organism / Antimicrobial Agent	No. of isolates and % susceptible / % resistant[a] rate: 2002	2003	2004	2005	2006	2007	2008	2009	2010
E. faecalis									
No. of strains	362	564	604	802	708	667	734	696	785
Daptomycin	100.0 / -	100.0 / -	99.8 / -	100.0 / -	100.0 / -	100.0 / -	100.0 / -	99.9 / -	100.0 / -
Vancomycin	97.2 / 2.8	96.1 / 3.9	97.7 / 2.3	95.8 / 4.2	95.9 / 4.1	95.4 / 4.6	93.6 / 6.4	97.1 / 2.9	96.7 / 3.3
Teicoplanin	98.9 / 1.1	98.6 / 1.4	98.7 / 1.3	97.6 / 2.4	97.5 / 2.5	96.1 / 3.9	95.4 / 4.6	97.1 / 2.3	97.3 / 2.7
E. faecium									
No. of strains	74	210	250	351	390	410	433	385	474
Daptomycin	98.7 / -	100.0 / -	100.0 / -	100.0 / -	100.0 / -	100.0 / -	99.1 / -	99.5 / -	99.2 / -
Vancomycin	35.1 / 64.9	31.9 / 68.1	30.4 / 69.6	29.9 / 70.1	26.4 / 73.6	25.9 / 74.1	22.4 / 77.6	21.6 / 78.4	20.9 / 79.1
Teicoplanin	41.9 / 58.1	35.9 / 64.1	32.4 / 67.6	31.6 / 68.4	26.9 / 73.1	26.3 / 73.7	23.3 / 76.7	23.6 / 76.4	22.6 / 77.4

a. Criteria as published by the CLSI [2011] and EUCAST [2011]

CONCLUSIONS

- Daptomycin demonstrated sustained antimicrobial activity against this large collection of clinical enterococci (including VRE) and streptococci (β-haemolytic and viridians group) from numerous USA medical centres over the last nine years.
- Greater than 99.83% of enterococci and >99.91% of streptococci were susceptible to daptomycin among the 14,044 USA strains tested.
- Daptomycin activity was not adversely influenced by resistance to vancomycin or teicoplanin among *E. faecalis* or *E. faecium*.

DISCLOSURE

CUBICIN® (daptomycin for injection) is not indicated for the treatment of enterococci or streptococci other than *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subspecies *equisimilis* and vancomycin-susceptible *E. faecalis* causing complicated skin and skin structure infections.

SELECTED REFERENCES

1. Clinical and Laboratory Standards Institute (2009). *M07-A8. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard.* eighth edition Wayne, PA: CLSI.
2. Clinical and Laboratory Standards Institute (2011). *M100-S21. Performance standards for antimicrobial susceptibility testing: 21st informational supplement.* Wayne, PA: CLSI.
3. Cubicin Package Insert (2009) Available at http://www.cubicin.com/pdf/PrescribingInformation.pdf; accessed on June 2009.
4. EUCAST (2011). Breakpoint tables for interpretation of MICs and zone diameters. Version 1.3, January 2011. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed: March 18, 2011.
5. Levine DP (2008) Clinical experience with daptomycin: bacteraemia and endocarditis. *J Antimicrob Chemother* 62 (Suppl 3):iii35-39.
6. Sader HS, Fey PD, Fish DN, Limaye A, Pankey G, Rahal J, Rybak M, Snydman D, Steed L, Waites K, Jones RN (2009) Evaluation of vancomycin and daptomycin potency trends ("MIC creep") against methicillin-resistant *Staphylococcus aureus* collected in nine United States medical centers over five years (2002- 2006). *Antimcrob Agents Chemother* 53(10):4127-4132.

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