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ANTIMICROBIAL SUSCEPTIBILITY OF DAPTOMYCIN AND COMPARATOR AGENTS TESTED AGAINST METHICILLIN-RESISTANT *S. AUREUS* (MRSA) AND VANCOMYCIN-RESISTANT ENTEROCOCCI (VRE): ANALYSIS OF A FIVE-YEAR TREND IN USA MEDICAL CENTRES (2005-2009)

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ABSTRACT (REVISED)

Background: Daptomycin (DAP) was approved by the USA-FDA for treating complicated skin and skin structure infections in 2003 and *S. aureus*-associated bacteremia and right-sided endocarditis in 2006; and has increasingly been used for these indications worldwide. We evaluated DAP activity trends against MRSA and VRE in a 5-year period (2005-2009) following regulatory release for USA clinical use.

Methods: Consecutive, unique patient strains of clinical significance were collected in 31 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: A total of 18,939 *S. aureus* (10,156 [53.6%] MRSA), 3,607 *E. faecalis* (EF; 161 [4.5%] VRE) and 1,968 *E. faecium* (EFM; 1,474 [74.9%] VRE) were evaluated. DAP-S rates were 99.94, 99.97 and 99.70% for *S. aureus*, EF and EFM, respectively. Among MRSA, only 11 (0.11%) DAP-non-S isolates were observed with no increasing tendency over the study period; while among VRE only 2 DAP-non-S isolates (both EFM; 0.14% of VR-EFM) were identified (**Table**). Vancomycin (VAN)-S and VRE exhibited very similar DAP MIC distributions. DAP was very active against VAN-resistant EF ($MIC_{50/90}$, 0.5-1/1-2 µg/ml; MIC range, 0.25-2 µg/ml). VAN ($MIC_{50/90}$, 1/1µg/ml; 100.0% S) and linezolid ($MIC_{50/90}$, 1/2 µg/ml; >99.9% S) also remained active against MRSA overall but were two- to four-fold less potent than DAP.

Conclusion: DAP demonstrated sustained activity against an extensive collection of clinical isolates of MRSA and VRE from numerous USA medical centres over the last five years. More than 99.9% of strains were S to DAP, which was more potent compared to vancomycin and linezolid against MRSA. DAP activity was not adversely influenced by resistance to oxacillin among *S. aureus* or resistance to vancomycin among enterococci.

Year (no.)	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	MIC range	No. (%) of daptomycin-non-S strains
MRSA (10,156)				
2005 (1,835))	0.25	0.5	≤0.06 - 2	1 (0.1)
2006 (2,011)	0.25	0.5	≤0.06 – 2	1 (<0.1)
2007 (2150))	0.25	0.5	≤0.06 – 2	1 (<0.1)
2008 (2363)	0.25	0.5	≤0.06 – 4	7 (0.4)
2009 (1,797)	0.5	0.5	≤0.06 - 2	1 (<0.1)
VRE(*E. faecium*; 1,474)				
2005 (246)	2	4	0.25 - 4	0 (0.0)
2006 (286)	1	2	0.25 – 4	0 (0.0)
2007 (304)	2	2	0.12 – 4	0 (0.0)
2008 (336)	2	4	≤0.06 – 8	2 (0.6)
2009 (302)	2	4	0.12 - 4	0 (0.0)

S=susceptible; MRSA=methicillin-resistant *Staphylococcus aureus*; VRE=vancomycin-resistant enterococcus.

INTRODUCTION

Staphylococcus aureus and enterococci are extremely important pathogens causing serious infections in the hospital environment. These organisms are usually 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) and by the European Medicines Agency (EMEA) for the treatment of complicated skin and skin structure infections (cSSSI) 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 MRSA and vancomycin-non-susceptible enterococci (VRE) over a 5-year period (2005-2009) following regulatory release for USA clinical use.

METHODS

Bacterial Isolates

- In the Daptomycin ACTIV™ Surveillance Program, consecutive unique patient strains of clinical significance were collected between January 2005 and December 2009 in 31 USA medical centers.
- The isolates were collected mainly from bloodstream infections and cSSSI 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: 18,939 *S. aureus* (53.6% MRSA), 3,607 *E. faecalis* (4.5% VRE), and 1,968 *E. faecium* (74.9% VRE).

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 Mueller-Hinton broth adjusted to contain physiological levels of calcium (50 mg/L) when testing daptomycin. CLSI and EUCAST interpretive criteria were used to categorize the isolates as susceptible, intermediate and resistant.
- A daptomycin susceptibility breakpoint of ≤1 µg/ml was applied for *S. aureus*, while ≤ 4 µg/ml was used for the enterococcal results, as recommended by the CLSI and the USA-FDA.
- EUCAST has established daptomycin susceptible and resistant breakpoints for *S. aureus* (≤1 and ≥2 µg/ml, respectively), but has not published daptomycin breakpoints for enterococcal strains.
- The following quality control organisms were concurrently tested: *S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212.

RESULTS

- MRSA rates remained somewhat stable during the study period. The overall occurrence of MRSA increased slightly from 51.3% in 2005 to 57.4% in 2008, but decreased to 51.0% in 2009 (**Figure 1**).
- Daptomycin was very active against 10,156 MRSA strains tested ($MIC_{50/90}$, 0.25/0.5 µg/ml; **Table 1**). Only 11 (0.11%) daptomycin-non-susceptible isolates were observed with no increasing tendency over the study period (**Table 2**). Vancomycin ($MIC_{50/90}$, 1/1µg/ml) and linezolid ($MIC_{50/90}$, 1/2 µg/ml) also remained very active against MRSA overall, but were two- to four-fold less potent than daptomycin (**Table 1**).
- VRE rates increased from 4.2% in 2005 to 6.4% in 2008 among *E. faecalis*; however, a substantial decrease to 2.9% was observed in 2009 (**Figure 2**). The majority (60 to 80%) of vancomycin-resistant *E. faecalis* isolates were also resistant to teicoplanin (VanA phenotype; **Table 1**), especially using EUCAST breakpoint criteria.
- Among *E. faecium*, VRE rates increased from 70.1% in 2005 to 78.4% in 2009 and >98% of VRE strains were also resistant to teicoplanin (**Table 1** and **Figure 3**). Only two daptomycin-non-susceptible isolates (0.1%) were observed among VRE (**Table 4**), both occurring in 2008.
- Vancomycin-susceptible and -resistant enterococci exhibited very similar daptomycin MIC distributions and no increasing tendency of daptomycin resistance over the study period was observed (**Tables 3 and 4**).

RESULTS

Table 1. Comparison of *in vitro* Activity of Daptomycin and Selected Antimicrobial Agents Tested Against Methicillin-resistant *Staphylococcus aureus* (MRSA) and Vancomycin-non-susceptible enterococci

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI* %S / %R	EUCAST* %S / %R
MRSA (10,156)					
Daptomycin	0.25	0.5	≤0.06 – 4	99.9 / -	99.9 / 0.1
Clindamycin	≤0.25	>2	≤0.25 – >2	60.8 / 38.9	60.4 / 39.2
Erythromycin	>2	>2	≤0.25 – >2	6.4 / 93.3	6.5 / 93.3
Levofloxacin	>4	>4	≤0.5 – >4	27.2 / 71.4	27.2 / 71.4
Linezolid	1	2	0.12 – >8	99.9 / 0.1	99.9 / 0.1
Tetracycline	≤2	≤2	≤2 – >8	94.1 / 5.5	93.2 / 6.8
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	98.0 / 2.0	98.0 / 2.0
Vancomycin	1	1	0.25 – 4	>99.9 / 0.0	>99.9 / <0.1
Vancomycin-non-susceptible *E. faecalis* (161					
Daptomycin	1	2	≤0.06 – 2	100.0 / -	- / -
Ampicillin	≤1	2	≤1 – >16	98.1 / 1.9	98.1 / 1.9
Levofloxacin	>4	>4	1 – >4	2.5 / 96.3	- / -
Linezolid	1	2	0.5 – >8	99.4 / 0.6	99.4 / 0.6
Teicoplanin	>16	>16	≤2 – >16	34.2 / 63.4	31.7 / 68.3
Vancomycin	>16	>16	8 – >16	0.0 / 90.7	0.0 / 100.0
Vancomycin-non-susceptible *E. faecium* (1,474)					
Daptomycin	2	2	≤0.06 – 8	99.9 / -	- / -
Ampicillin	>16	>16	≤1 – >16	0.3 / 99.7	0.1 / 99.7
Levofloxacin	>4	>4	≤0.5 – >4	0.2 / 99.8	- / -
Linezolid	1	2	0.5 – >8	97.6 / 2.2	97.8 / 2.2
Quinupristin/dalfopristin	0.5	1	≤0.25 – >2	96.2 / 1.6	96.2 / 1.6
Teicoplanin	>16	>16	≤2 – >16	2.5 / 87.9	1.6 / 98.4
Vancomycin	>16	>16	8 – >16	0.0 / 99.3	0.0 / 100.0

*Criteria as published by the CLSI [2010] and EUCAST [2010].
S=susceptible; R=resistant.

Table 2. Frequencies of Occurrence of Daptomycin MIC Values for *S. aureus* Strains

Phenotype / year (no. of isolates)	No. of isolates (%) inhibited at daptomycin MIC of (µg/ml): ≤0.06	0.12	0.25	0.5	1	2	4
MRSA							
2005 (1,835)	1 (≤0.1)	26 (1.4)	1,136 (61.9)	656 (35.8)	15 (0.8)	1 (0.05)	-
2006 (2,011)	3 (0.2)	65 (3.2)	1,565 (77.8)	371 (18.5)	6 (0.3)	1 (0.05)	-
2007 (2,150)	2 (0.1)	72 (3.4)	1,737 (80.8)	327 (15.2)	11 (0.5)	1 (0.05)	-
2008 (2,363)	-	34 (1.4)	1,433 (60.6)	862 (36.5)	27 (1.1)	6 (0.3)	1 (0.04)
2009 (1,797)*	-	19 (1.1)	679 (37.8)	1,064 (59.2)	34 (1.9)	1 (0.06)	-
All (10,156)	6 (0.06)	216 (2.1)	6,550 (64.5)	3,279 (32.3)	94 (0.9)	10 (0.1)	1 (0.01)
MSSA							
All (8,783)	17 (0.2)	455 (5.2)	6,359 (77.8)	1,914 (21.8)	37 (0.4)	1 (0.01)	-

*The increase in the occurrences of daptomycin MIC of 0.5 µg/ml in 2009 compared to previous years was caused by low content of calcium in one of the lots of MIC plates used during the year. All daptomycin MIC results for the QC organisms were within the CLSI acceptable ranges and no increase in the occurrences of MIC values of 1 µg/ml or higher were observed.

Table 3. Frequencies of Occurrence of Daptomycin MIC Values for *E. faecalis* Strains

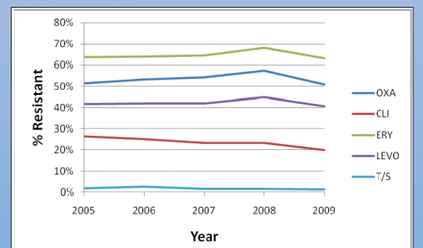
Phenotype / year (no. of isolates)	No. of isolates (%) inhibited at daptomycin MIC of (µg/ml): ≤0.06	0.12	0.25	0.5	1	2	4	8
Vancomycin-resistant								
2005 (34)	-	-	1 (2.9)	17 (50.0)	12 (35.3)	4 (11.8)	-	-
2006 (29)	-	-	3 (10.3)	16 (55.2)	9 (31.0)	1 (3.5)	-	-
2007 (31)	-	-	1 (3.2)	15 (48.4)	13 (41.9)	2 (6.5)	-	-
2008 (47)	1 (2.1)	-	-	14 (29.8)	29 (61.7)	3 (6.4)	-	-
2009 (20)*	1 (5.0)	-	-	2 (10.0)	10 (50.0)	7 (35.0)	-	-
All (161)	2 (1.2)	-	5 (3.1)	64 (39.8)	73 (45.3)	17 (10.6)	-	-
Vancomycin-susceptible								
All (3,446)	9 (0.3)	28 (0.8)	141 (4.1)	1,315 (38.2)	1,635 (47.5)	305 (8.9)	12 (0.4)	1 (0.3)

*The increase in the occurrences of daptomycin MIC of 2 µg/ml in 2009 compared to previous years was caused by low content of calcium in one of the lots of MIC plates used during the year. All daptomycin MIC results for the QC organisms were within the CLSI acceptable ranges and no increase in the occurrences of MIC values of 4 µg/ml or higher were observed.

Table 4. Frequencies of Occurrence of Daptomycin MIC Values for *E. faecium* Strains

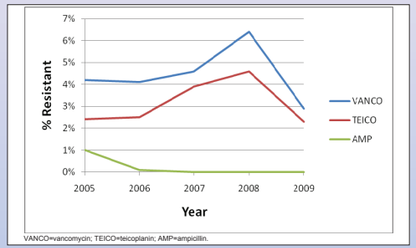
Phenotype / year (no. of isolates)	No. of isolates (%) inhibited at daptomycin MIC of (µg/ml): ≤0.06	0.12	0.25	0.5	1	2	4	8	>8
Vancomycin-resistant									
2005 (246)	-	-	1 (0.4)	21 (8.5)	61 (24.8)	129 (52.4)	34 (13.8)	-	-
2006 (286)	-	-	4 (1.4)	25 (8.7)	150 (52.5)	103 (36.0)	4 (1.4)	-	-
2007 (304)	-	-	5 (1.6)	8 (2.6)	117 (38.5)	163 (53.6)	11 (3.6)	-	-
2008 (336)	2 (0.6)	2 (0.6)	5 (1.5)	6 (1.8)	87 (25.9)	213 (63.4)	19 (5.7)	2 (0.6)	-
2009 (302)	-	-	-	7 (2.3)	61 (20.2)	198 (65.6)	36 (11.9)	-	-
All (1,474)	2 (0.1)	2 (0.1)	15 (1.0)	67 (4.6)	476 (32.3)	806 (54.7)	104 (7.1)	2 (0.1)	-
Vancomycin-susceptible									
All (494)	-	3 (0.6)	7 (1.4)	25 (5.1)	148 (30.0)	257 (52.0)	50 (10.1)	3 (0.6)	1 (0.2)

Figure 1. Five Year Trend of Antimicrobial Resistance Rates Among *S. aureus* from USA Medical CentersStrains



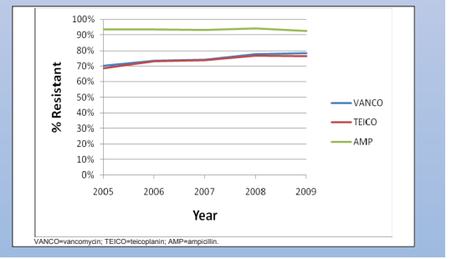
OXA=oxacillin; CLI=clindamycin; ERY=erythromycin; LEVO=levofloxacin; T/S=trimethoprim/sulfamethoxazole.

Figure 2. Five Year Trend of Antimicrobial Resistance Rates Among *E. faecalis* Strains from USA Medical Centers



VANCO=vancomycin; TEICO=teicoplanin; AMP=ampicillin.

Figure 3. Five Year Trend of Antimicrobial Resistance Rates Among *E. faecium* Strains from USA Medical Centers



VANCO=vancomycin; TEICO=teicoplanin; AMP=ampicillin.

CONCLUSIONS

- Daptomycin demonstrated sustained activity against an extensive collection of clinical isolates of MRSA and VRE from numerous USA medical centers over the last five years.
- More than 99.9% of strains were susceptible to daptomycin, which was more potent when compared to vancomycin and linezolid against MRSA.
- Daptomycin activity was not adversely influenced by resistance to oxacillin among *S. aureus* or resistance to vancomycin and teicoplanin among enterococci.

Acknowledgments

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