ICAAC & IDSA 2008
C1-141

ANTIMICROBIAL ACTIVITY OF DAPTOMYCIN AND COMPARATORS TESTED AGAINST *STAPHYLOCOCCUS AUREUS* FROM 20 USA HOSPITALS IN 2005-2008: EVALUATION OF POTENCY TRENDS

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ABSTRACT

Background: Daptomycin (DAP) is a lipopeptide with potent bactericidal activity against Gram-positive pathogens, approved by USA-FDA for treatment of skin and soft tissue infection in 2003. We evaluated DAP potency trends in a 4-year period (2005-2008) following USA-FDA release for clinical use.

Methods: Consecutive, unique patient strains of clinical significance were collected in 20 USA hospitals 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: Among 11,243 strains tested, 53.7% were resistant (R) to oxacillin (OXA). OXA R increased from 51.8% in 2005 to 58.8% in 2008. R to other antimicrobials included: erythromycin (65.8%), levofloxacin (43.9%), clindamycin (24.8%) and trimethoprim-sulfamethoxazole (2.0%); these R remained stable over the study period. The highest DAP MIC observed was 2 µg/ml (3 strains). No significant variation in DAP potency was noted against OXA-R or OXA-S *S. aureus* (SA) (Table). Linezolid (LZD; $MIC_{50/90}$, 1/2 µg/ml, >99.9% S) and vancomycin (VAN; $MIC_{50/90}$, 1/1 µg/ml, >99.9% S) were also very active, but four-fold less potent than DAP ($MIC_{50/90}$, 0.25/0.5 µg/ml).

Year (no. tested)	% inhibited at DAP MIC (µg/ml) of: ≤0.12	0.25	0.5	1	2	No. of DAP non-S strains
MRSA						
2005 (1731)	1.7	66.9	29.3	0.5	0.06	1
2006 (1885)	3.2	78.4	16.1	0.3	0.05	1
2007 (1721)	3.7	80.9	12.9	0.4	0.0	0
2008 (701)	1.1	75.8	22.3	0.5	0.06	1
All years (6038)	2.7	73.1	23.7	0.6	0.1	3
All MSSA (5205)	6.5	78.1	15.2	0.2	0.0	0

Conclusions: DAP was highly active against SA and its activity remained stable across the 4-year period evaluated (2005-2008) using reference methods. Decrease in DAP potency ("MIC creep") has not been observed since USA-FDA approval and widespread clinical use. R to OXA increased during the same period but did not adversely influence DAP activity. R to LZD, VAN and DAP remain uncommon among SA isolated in USA hospitals.

INTRODUCTION

Staphylococcus aureus, an important cause of infection in hospitalized patients, principally causes bacteremia, pneumonia and skin and soft tissue infections. Moreover, infections caused by methicillin (oxacillin)-resistant *S. aureus* (MRSA) strains are associated with longer hospital stay, more days of antimicrobial therapy and higher healthcare-associated costs than infections caused by methicillin-susceptible *S. aureus* (MSSA) strains. Vancomycin remains the standard for treating most MRSA infections; however, concerns over increases in the rates of heteroresistance and tolerance to this agent, combined with its compromised safety and clinical shortcomings have motivated the increasing use of newer agents.

INTRODUCTION

Daptomycin is a novel lipopeptide with potent in vitro activity against Gram-positive cocci. Daptomycin was approved by the United States (USA) Food and Drug Administration (FDA) in late 2003 for the treatment of complicated skin and skin structure infections (cSSSI) caused by MSSA and MRSA, groups A and B β-haemolytic streptococci, and for vancomycin-susceptible *Enterococcus faecalis*. In addition, this compound was later approved for the treatment of *S. aureus* bacteremia, including right-sided endocarditis.

In the present study, we evaluated daptomycin potency trends in the 4-year period (2005-2008) following USA-FDA release for clinical use.

MATERIALS AND METHODS

Bacterial Isolates: The Daptomycin Surveillance Program was established in 2002 with the objective to monitor the in vitro activity of daptomycin and most antimicrobials agents used to treat gram-positive infections. The program collects Gram-positive bacterial isolates from documented clinical infections, mainly cSSSI and bloodstream infections (daptomycin not used for the pneumonia indication). The isolates evaluated in the present study were collected from 2005 to 2008 in 20 medical centers located in the USA according to a common protocol. All hospitals participated in the study during the entire period of the study. The strains were identified locally and forwarded to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa) for confirmation of species identification, when necessary, and reference susceptibility testing.

Susceptibility Testing: The strains were susceptibility tested against daptomycin and numerous comparator agents by reference broth microdilution methods performed according to Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) documents. All strains were tested in validated broth microdilution panels manufactured by TREK Diagnostics (Cleveland, OH). Mueller-Hinton broth adjusted to contain physiological levels of calcium (50 mg/L) was used when testing daptomycin. Daptomycin susceptible breakpoint approved by USA-FDA and CLSI for staphylococci (≤1 µg/ml) was applied. The following quality control (QC) organisms were concurrently tested: *Enterococcus faecalis* ATCC 29212, *S. aureus* ATCC 29213 and *Streptococcus pneumoniae* ATCC 49619. All QC results were within published ranges.

RESULTS

- Daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/ml), vancomycin ($MIC_{50/90}$, 1/1 µg/ml) and linezolid ($MIC_{50/90}$, 1/2 µg/ml) were highly active (>99.9% susceptibility) against the *S. aureus* collection (2005-2008) evaluated. Daptomycin was the most potent (lowest MIC_{50} and MIC_{90}) among these active compounds (**Table 1**).

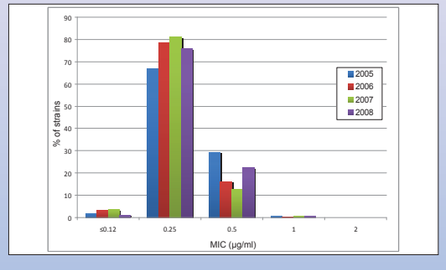
Table 1. Antimicrobial activity of daptomycin and comparator agents tested against *S. aureus* strains from 20 USA hospitals (2005-2008).

Organism/Antimicrobial agent (no. tested)	MIC_{50}	MIC_{90}	% Susceptible	% Resistant
Oxacillin-susceptible (5,205)				
Daptomycin	0.25	0.5	100.0	-*
Clindamycin	≤0.25	≤0.25	94.7	5.1
Erythromycin	≤0.25	>2	68.7	30.7
Levofloxacin	≤0.5	≤0.5	91.3	8.1
Linezolid	1	2	100.0	-
Quinupristin/dalfopristin	≤0.25	0.5	99.9	0.0
Tetracycline	>2	≤2	96.0	3.2
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	98.4	1.6
Vancomycin	1	1	100.0	0.0
Oxacillin-resistant (6,038)				
Daptomycin	0.25	0.5	>99.9	-
Clindamycin	≤0.25	>2	58.1	41.8
Erythromycin	>2	>2	5.6	94.2
Levofloxacin	>4	>4	25.7	72.6
Linezolid	1	2	>99.9	-
Quinupristin/dalfopristin	0.5	0.5	99.8	<0.1
Tetracycline	≤2	≤2	93.3	5.8
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	97.7	2.3
Vancomycin	1	1	>99.9	<0.1

* No breakpoint has been established by CLSI.

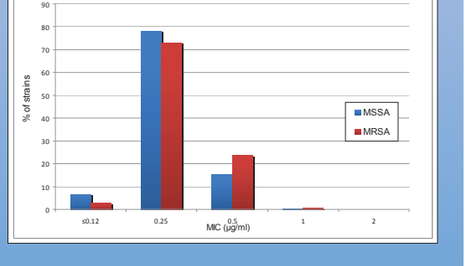
- Oxacillin-susceptible strains showed high rates of susceptibility (>90%) to all agents tested, except erythromycin (68.7% susceptibility); while MRSA showed high rates of resistance to clindamycin (41.8%), erythromycin (94.2%) and levofloxacin (72.6%). Furthermore, all strains non-susceptible to daptomycin, linezolid and vancomycin were MRSA.
- Daptomycin activity did not vary significantly and no trend toward higher resistance was observed during the 4-year study interval (**Figure 1**).

Figure 1. Yearly frequency of daptomycin MIC values among *S. aureus* collected in 20 USA medical centers.



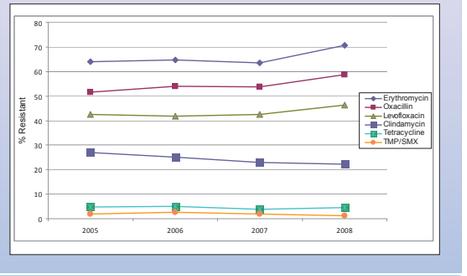
- Daptomycin activity was not adversely influenced by resistance to oxacillin (**Figure 2**).

Figure 2. Daptomycin MIC distributions among methicillin-susceptible and -resistant *S. aureus* collected in 20 USA medical centers (2005-2008).



- During the study period (2005 - 2008), resistance rates increased for the following antimicrobial agents: erythromycin (from 64.1 to 70.8%), oxacillin (51.7 to 58.8%) and levofloxacin (42.6 to 46.4%). In contrast, resistance to clindamycin decreased from 27.1% in 2005 to 22.2% in 2008 (**Figure 3**).

Figure 3. Variation of *S. aureus* resistance rates to selected antimicrobial in the 2005-2008 period



CONCLUSIONS

- Daptomycin was highly active against *S. aureus* and its activity remained stable across the 4-year period evaluated (2005-2008) using reference CLSI methods.
- Decreases in daptomycin potency ("MIC creep") were not observed since USA-FDA approval and widespread clinical use of these agents.
- Resistance to oxacillin increased during the same period, but did not adversely influence daptomycin activity.
- Resistance to daptomycin (three strains among 11,243 isolates; all at 2 µg/ml), linezolid and vancomycin remains very uncommon among *S. aureus* isolated in USA hospitals.

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This study was funded by Cubist Pharmaceuticals.