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ANTIMICROBIAL ACTIVITY OF DAPTOMYCIN AND SELECTED COMPARATORS TESTED AGAINST *STAPHYLOCOCCUS AUREUS* CAUSING BLOODSTREAM INFECTIONS IN DIALYSIS PATIENTS

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ABSTRACT

BACKGROUND: Dialysis patients (DPT) are especially vulnerable to infections, frequently those caused by multidrug-resistant *S. aureus* (SA). The objective of this study was to evaluate the antimicrobial susceptibility (S) patterns of SA causing bloodstream infections (BSI) in DPT when compared to those causing BSI in other patient population.

METHODS: As part of the daptomycin (DAP) Surveillance Program, 606 SA causing BSI in DPT were collected from 43 hospitals in North America and Europe in 2002-2006. Isolates were S tested against DAP and various comparators by CLSI broth microdilution method. Ca^{++} content of the broth was adjusted (50 mg/L) for testing DAP. S patterns of DPT strains were compared to those of 1,212 SA strains (2:1) causing BSI in non-DPT in the same hospitals and time period as well as to those of all SA strains from BSI.

RESULTS: Among all SA strains collected from BSI, 5% were from DPT. DAP was highly active against SA from DPT (MIC_{50}/MIC_{90}, 0.25 / 0.5 µg/ml). Only 1 DAP non-S strain was identified, and DAP activity was not adversely affected by oxacillin-R. Vancomycin (VAN; MIC_{50}/MIC_{90}, 1 / 1 µg/ml) and linezolid (LZD; MIC_{50}/MIC_{90}, 2 / 2 µg/ml) showed similar potency and rates of S (99.8-100.0% S), but were four- to eight-fold less potent than DAP. The S patterns of DPT strains were very similar to those of non-DPT and BSI strains from other patients (*see* **Table**).

	% of SA strains S (no. tested)		
Antimicrobials	DP (606)	Control (1,212)	BSI (12,163)
DAP	99.8 (1)[a]	100.0	>99.9 (6)[a]
Oxacillin	60.4	60.6	61.8
Clindamycin	78.5	79.1	75.2
Levofloxacin	60.9	59.9	62.0
Mupirocin	94.2[b]	95.7[b]	96.0[b]
LZD	99.8 (1)[a]	100.0	>99.9 (2)[a]
VAN	100.0	100.0	>99.9 (4)[a]

a. Number of non-susceptible isolates in parenthesis.
b. MIC, ≤8 µg/ml.

CONCLUSIONS: DAP exhibited sustained activity against a large collection of SA collected from BSI, including strains from DPT. Due to its excellent anti-SA spectrum, high potency and rapid bactericidal activity, DAP may represent an excellent option for treatment of BSI caused by SA in these at-risk patients.

INTRODUCTION

Patients on long-term hemodialysis are at a significantly high risk for catheter-related bloodstream infections (BSI). These infections are caused mainly by Gram-positive organisms, especially *Staphylococcus aureus*, which has been associated with the most devastating metastatic complications among dialysis patients due to its predilection to adhere to heart valves and bone. Furthermore, vascular access-related BSI and related complications requiring hospitalization, account for nearly one-third of the cost of end stage renal disease management, with reported mortality rates of 12-26%.

Daptomycin is a novel lipopeptide antimicrobial agent with potent in vitro activity against Gram-positive cocci. Daptomycin does not exhibit cross resistance with other known classes of antimicrobials and also has a low risk for development of spontaneous mutational resistance. Indeed, daptomycin has been shown to be active against MRSA, *S. aureus* resistant to linezolid or quinupristin/dalfopristin, vancomycin-resistant enterococci (VRE), and macrolide-resistant streptococci.

Daptomycin was approved by the United States Food and Drug Administration (US-FDA) and by the European Medicines Agency (EMEA) for the treatment of complicated skin and skin structure infections (SSSI) caused by MSSA and MRSA, groups A and B β-haemolytic streptococci, and for vancomycin-susceptible *Enterococcus faecalis*. This compound has also been recently approved for the treatment of *S. aureus* BSI including right-sided endocarditis.

In the present study, we evaluated the antimicrobial susceptibility patterns of *S. aureus* causing BSI in dialysis patients compared to those causing BSI in other patient populations.

MATERIALS AND METHODS

Bacterial isolates: As part of the Daptomycin Surveillance Program, 606 *S. aureus* causing BSI in dialysis patients were collected from 43 hospitals in North America and Europe in 2002-2006. Susceptibility patterns of strains from dialysis patients were compared to those of 1,212 *S. aureus* strains (2:1 randomization) causing BSI in non-dialysis patients. For each strain from a dialysis patient, two strains from BSI in non-dialysis patients hospitalized in the same hospital and time period were included as the control group. A third group of strains used for comparison included all *S. aureus* strains collected by the JMI Laboratories (North Liberty, IA) from BSI in North American and European medical centers in the 2002-2006 period (12,163 strains).

Susceptibility testing: Daptomycin and more than 20 comparator agents were tested using the Clinical Laboratory Standards Institute (CLSI) M7-A7 broth microdilution method. All strains were tested in validated, broth microdilution panels manufactured by TREK Diagnostics (Cleveland, OH). Mueller-Hinton Broth (MHB) adjusted to contain physiological levels of calcium (50 mg/L) was used when testing daptomycin. US-FDA and CLSI approved daptomycin susceptibility breakpoint for *S. aureus* (≤1 µg/ml) were applied. The following quality control organisms were concurrently tested: *E. faecalis* ATCC 29212, *S. aureus* ATCC 29213 and *Streptococcus pneumoniae* ATCC 49619.

RESULTS

- Among all *S. aureus* strains collected from BSI in the Daptomycin Surveillance Program, 5% were from dialysis patients.
- Daptomycin was highly active against *S. aureus* causing infections in dialysis patients (MIC_{50}, 0.25 µg/ml; MIC_{90}, 0.5 µg/ml). Only one strain showed decreased susceptibility to daptomycin (MIC of 2 µg/ml; **Table 1**).
- Daptomycin MIC distribution of *S. aureus* BSI strains from dialysis patients was very similar to those of the other two groups of *S. aureus* strains evaluated (control group and all BSI strains; **Table 1**).
- Daptomycin activity was not adversely affected by oxacillin resistance.
- Vancomycin (MIC_{50} and MIC_{90} of 1 µg/ml) and linezolid (MIC_{50} and MIC_{90} of 2 µg/ml) showed similar potency and susceptibility rates (99.8-100.0%), but were four- to eight-fold less active than daptomycin (**Table 2**).
- The susceptibility patterns of BSI strains from dialysis patients were comparable to those of non-dialysis patients (**Table 2**).

RESULTS

Table 1. Daptomycin MIC distributions of *S. aureus* isolates causing BSI in dialysis patients in comparison to those causing BSI in non-dialysis patient populations.

	No. of isolates (cumulative %) inhibited at daptomycin MIC (µg/ml) of:					
	≤0.12	0.25	0.5	1	2	4
Dialysis patients (606)	28 (4.6)	412 (72.6)	159 (98.8)	6 (99.7)	1 (100.0)	-
Control group[a] (1,212)	55 (4.5)	869 (76.2)	282 (99.5)	6 (100.0)	-	-
Bloodstream infection[b] (12,192)	552 (4.5)	8,569 (74.8)	2,979 (99.3)	85 (>99.9)	5 (>99.9)	1 (100.0)

a. For each strain from a dialysis patient, two strains (2:1) from BSI in non-dialysis patients hospitalized in the same hospital and time period.
b. Includes all *S. aureus* strains collected from BSI in North America and Europe from January 2002 to December 2006.

Table 2. Antimicrobial susceptibility pattern of *S. aureus* causing BSI in dialysis patients in comparison to those causing BSI in non-dialysis patients.

	Dialysis (606)		Control (1,212)		BSI (12,185)	
Antimicrobial agents	MIC_{90}	% susceptible	MIC_{90}	% susceptible	MIC_{90}	% susceptible
Daptomycin	0.5	99.8[a]	0.5	100.0	0.5	>99.9
Oxacillin	>2	60.4	>2	60.6	>2	61.8
Erythromycin	>8	47.0	>8	45.7	>8	44.6
Clindamycin	>8	78.5	>8	79.0	>8	75.2
Levofloxacin	>4	60.9	>4	59.9	>4	62.0
Mupirocin	≤4	94.2[b]	≤4	95.7[b]	≤4	96.0[b]
Trimethoprim/sulfamethoxazole	≤0.5	98.2	≤0.5	97.3	≤0.5	97.0
Quinupristin/dalfopristin	0.5	99.7	0.5	99.5	0.5	99.8
Linezolid	2	99.8[c]	2	100.0	2	>99.9
Vancomycin	1	100.0	1	100.0	1	>99.9

a. One non-susceptible strain with daptomycin MIC at 2 µg/ml.
b. MIC ≤8 µg/ml.
c. One non-susceptible strain with linezolid MIC at 8 µg/ml.

CONCLUSIONS

- Daptomycin exhibited sustained activity against a large collection of *S. aureus* collected from BSI (2002-2006 sample), including strains from dialysis patients.
- Because of its excellent anti- *S. aureus* spectrum, high potency and rapid bactericidal activity, daptomycin represents an excellent option for treatment of BSI caused by *S. aureus* in at-risk patients such as those on dialysis.

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