Daptomycin resistance in methicillin-resistant *Staphylococcus aureus*: a report from Southern India

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Methicillin-resistant *Staphylococcus aureus* (MRSA) colonization or infection of the wound may cause MRSA bacteremia with increased mortality, making it important to treat the infection. The increasing prevalence of MRSA accentuates the need for an effective therapy.[1] Daptomycin is a cyclic lipopeptide antibiotic derived from *Streptomyces roseosporus*, which shows a potent bactericidal activity against most Gram-positive organisms including MRSA.[1,2] Daptomycin received FDA approval in 2003 and was launched overseas. However it was approved for use in India after over 4 years (in 2008) without conducting any clinical trial in Indian population.[3] Prior to this, a Sentry Antimicrobial Surveillance Program (2006-2007) performed in 14 medical center in 13 Indian cities observed 100% susceptibility of the MRSA strains to Daptomycin.[1] Following its introduction, limited data is available on the level of resistance to daptomycin in MRSA strains in India, making it important to have knowledge of the contemporary susceptibility levels.

The present study was conducted in St. John's Medical College Hospital, a tertiary care multi-specialty hospital in Bangalore, India catering to patients of all socio-economic classes. We retrospectively determined the minimum inhibitory concentration (MIC) of daptomycin for clinically relevant, non-repetitive 30 MRSA and 20 methicillin-sensitive *Staphylococcus aureus* (MSSA) isolates randomly selected from 1615 *Staphylococcus aureus* isolates obtained from pus and wound swab samples (n=6687) submitted to the microbiology laboratory for aerobic culture and sensitivity profiling during January 2011 to December 2011. Among the 30 strains of MRSA, 22 strains were from hospital-acquired (HA)-MRSA infection and 8 strains were from community-acquired (CA)-MRSA infection.

The majority of the patients harboring these MRSA strains were male (70%) and belonged to the age groups 21-40 years (46.7%), followed by 41-60 years (26.7%), ≤20 years (16.7%) and 61-80 years (10%). The patients harboring the studied MSSA strains were predominantly females (60%) and belonging to the age groups 21-40 years (45%), followed by 41-60 years (25%), 61-80 years and ≤20 years (15% each).

Table 1. Antibiotic resistance pattern of the MRSA and MSSA clinical isolates

Antibiotics	MRSA (n=30)	MSSA (n=20)
Erythromycin	8 (27%)	6 (30%)
Tetracycline	5 (17%)	0
Co-trimoxazole	8 (27%)	5 (25%)
Chloramphenicol	2 (7%)	0
Rifampicin	1 (3%)	0
Ciprofloxacin	18 (60%)	10 (50%)
Gentamycin	13 (43%)	3 (15%)
Netilmicin	1 (3%)	1 (5%)
Amikacin	7 (23%)	1 (5%)
Vancomycin	2 (7%)	1 (5%)
Teicoplanin	0	0

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Table 2. Daptomycin minimum inhibitory concentration levels in MRSA and MSSA clinical isolates

Organisms	MIC levels of the isolates (µg/mL)						MIC range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	Suscept-ibility (%)
	≤0.19	0.25	0.38	0.5	1	≥2				
MRSA (n=30)	2	7	5	8	6	2	0.19-2	0.38	1	93.3
HA-MRSA (n=22)	1	4	4	7	4	2	0.19-2	0.5	1	90.9
CA-MRSA (n=8)	1	3	1	1	2	0	0.19-1	0.25	0.5	100
MSSA (n=20)	4	3	5	5	3	0	0.19-1	0.38	1	100

The antibiotic resistance patterns of these isolates were determined by Kirby-Bauer disc diffusion method as per CLSI guidelines. The MIC for daptomycin (range: 0.016-256 µg/mL) was performed by E-test (bioMérieux, SA, France) according to CLSI guidelines. ATCC 29213 *Staphylococcus aureus* strain was used as a control. Table 1 shows the antibiotic resistance pattern of the strains included in this study. Vancomycin resistance by disc diffusion method was observed in 7% of the MRSA (n=2) and 5% (n=1) of the MSSA strains. All the isolates were susceptible to teicoplanin. The MIC levels of daptomycin against the MRSA and MSSA clinical isolates studied are shown in the Table 2. The MIC value for *S. aureus* ATCC 29213 was within the range 0.38-0.5 µg/mL. Daptomycin resistance in MRSA strains was observed at a low level of 6.7% (2/30). All the MRSA strains showed a MIC_{50}/MIC_{90} of 0.38/1 µg/mL against daptomycin (MIC range: 0.19-2 µg/mL). Two HA-MRSA strains showed resistance to daptomycin (MIC: 2 µg/mL), retaining susceptibility to vancomycin. Daptomycin showed potent activity (MIC: ≤0.38 µg/mL) against vancomycin resistant MRSA (n=2) isolates. However since the MIC was not performed for vancomycin we could not ascertain whether these two strains were vancomycin resistant *Staphylococcus aureus* (VRSA) or vancomycin intermediate *Staphylococcus aureus* (VISA). It was further observed that the CA-MRSA strains (MIC_{50}/MIC_{90}: 0.25/0.5 µg/mL) were inhibited at two-fold lower MIC than HA-MRSA strains (MIC_{50}/MIC_{90}: 0.5/1 µg/mL). None of the twenty MSSA strains showed resistance to daptomycin (MIC_{50}/MIC_{90}: 0.38/1; range: 0.19-1 µg/mL).

Although the sample size was small, daptomycin showed a good potency, inhibiting 93% of the MRSA strains. Our data supports the previous studies, showing good activity of daptomycin against MRSA strains. Earlier studies from India have reported daptomycin resistance in MRSA strains ranging from 0% to 10%.[1,4-8] The studies reporting daptomycin resistance in Indian MRSA strains were from northern India (10%) and western India (6.25%).[7, 8] To our knowledge for the first time we are reporting daptomycin resistance in MRSA (6.7%) from Southern India.

With a well-documented safety profile and increased success rate in MRSA infection, daptomycin can be a viable therapeutic option for patients with MRSA wound infection. However in view of daptomycin resistant strains observed in our study we suggest that daptomycin MIC should be monitored to prevent treatment failure from possible emergence of strains with reduced susceptibility.

Authors' contribution statement SM and SG conceived and designed the experiments; AV performed the experiments: SG, AV and SM analyzed the data; SG and AV wrote the paper; all authors approved the final version of the manuscript.

Conflicts of interest All authors – none to declare.

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