*Original Article*

# Susceptibility of clinical methicillin-resistant Staphylococci isolates to new antibiotics

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## Abstract

Background: The treatment of methicillin-resistant staphylococcal infections has been a growing problem both in and out of hospitals for the past 30 years. Therefore, there is a need for other antibiotics as an alternative to glycopeptides in the treatment of methicillin-resistant staphylococcal infections. This study investigated the *in vitro* susceptibility of 49 methicillin-resistant *Staphylococcus aureus* (MRSA) and 59 methicillin-resistant coagulase negative staphylococci (MRCNS) clinical isolates to daptomiycin, telithromycin, tigecyclin, quinupristin/dalfopristin, and linezolid.

Methodology: The identification of the strains was made by conventional methods. Antibiotic susceptibility tests were performed according to CLSI. Methicillin resistance was determined by cefoxitin disk. Susceptibilities of the strains to daptomycin, quinupristin/dalfopristin, tigecycline, and vancomycin were performed using the E-test according to the recommendations of CLSI 2011 and the manufacturer.

Results: Two strains of MRCNS were resistant, and one was teicoplanin intermediate. It was found that one (2%) strain of MRSA and two (3%) strains of MRCNS were resistant to tigecyclin. Telithromycin resistance was detected in 33% of MRSA strains and 37% of MRCNS strains. Inducible clindamycin resistance was found in nine (18.4%) strains of MRSA and eighteen (30.5%) strains of MRCNS. All strains were susceptible to daptomiycin, quinupristin/dalfopristin, and linezolid.

Conclusions:Although it has recently been used, telithromycin has a high percentage of resistance; its use for methicillin-resistant staphylococcal strains, therefore, should be limited. Daptomycin and quinupristin/dalfopristin were found to be effective against MRSA and MRCNS strains and were concluded to be a good choice in the treatment of methicillin-resistant staphylococci.

**Key words:** daptomiycin; linezolid; quinupristin; dalfopristin; telithromycin; tigecycline

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## Introduction

Since the discovery of antibiotics, microorganisms have developed resistance mechanisms to them. Efforts have been made to overcome this problem by developing new classes of antibiotics, but eventually there was a hesitation in the development of antibiotics; many new antibiotics developed in the last ten years have been derived from modifications of existing antibiotics [6]. The most important problem in the treatment of staphylococcal infections is methicillin resistance. As methicillin-resistant staphylococci are also resistant to beta-lactams, there is a need for other antibiotics that can be an alternative to glycopeptides in the treatment of staphylococci infections. In the last ten years, new antibiotics such as daptomycin (lipopeptide), linezolid (oxazolidinones), quinupristin/dalfopristin (streptogramin combination), telithromycin (ketolide), and tigecycline (glycylcycline) have been developed. Of these, linezolid and daptomycin were among the antibiotics approved by the U.S. Food and Drug Administration (FDA) between 1998 and 2002 [2].

## Methodology

This study evaluated the *in vitro* susceptibilities of 49 methicillin-resistant *Staphylococcus aureus* (MRSA) and 59 methicillin-resistant coagulase-negative staphylococci (MRCNS) isolates to selected antibiotics. These isolates were isolated and identified by conventional methods from various clinical specimens (blood, abscess, pus, sterile body fluids, urine, etc.) between September 2007 and March 2009. The susceptibility of the isolates to daptomycin, telithromycin, tigecycline, quinupristin/dalfopristin, and linezolid was tested. Antibiotic susceptibility tests were performed according to the Clinical and Laboratory Standards Institute (CLSI) [7]. Methicillin resistance was determined by cefoxitin disk (30 µg, Oxoid, Basingstoke, UK) (55). Susceptibilities of the strains to daptomycin, quinupristin/dalfopristin,

**Table 1.** $MIC_{50}$ ve $MIC_{90}$ (µg/mL) values for daptomycin, quinupristin/dalfopristin, tigecycline, and vancomycin of MRSA and MRCNS strains.

| Antibiotics | MRSA (n=49) | | MRCNS (n=59) | |
|---|---|---|---|---|
| | $MIC_{50}$ | $MIC_{90}$ | $MIC_{50}$ | $MIC_{90}$ |
| Daptomycin | 0.25 | 0.50 | 0.50 | 0.50 |
| Quinupristin/dalfopristin | 0.50 | 0.75 | 0.75 | 0.50 |
| Tigecycline | 0.19 | 0.38 | 0.38 | 0.38 |
| Vancomycin | 1.50 | 1.50 | - | - |

**Table 2:** Resistance of MRSA and MRCNS strains to various antibiotics.

| Antibiotics | MRSA (n=49) | | MRCNS (n=59) | |
|---|---|---|---|---|
| | n | % | n | % |
| Penicillin G | 49 | 100 | 59 | 100 |
| Vancomycin | 0 | | 0 | |
| Teicoplanin | 0 | | 3 | 5 |
| Erithromycin | 29 | 59 | 53 | 90 |
| Clindamycin | 25 | 51 | 45 | 76 |
| Co-trimoxazole | 6 | 12 | 41 | 69 |
| Telithromycin | 16 | 33 | 22 | 37 |
| Tigecycline | 1 | 2 | 2 | 3 |
| Quinupristin/dalfopristin | 0 | | 0 | |
| Daptomycin | 0 | | 0 | |
| Linezolid | 0 | | 0 | |

tigecycline, and vancomycin were performed using the E-test (AB Biodisk, Solna, Sweden) according to the recommendations of the CLSI and the manufacturer. Strains with a minimal inhibitory concentration (MIC) value ≤ 0.5 µg/mL for tigecycline, ≤ 2 µg/mL for vancomycin, ≤ 1 µg/mL for daptomycin and quinupristin/dalfopristin were considered to be susceptible [7]. Susceptibility tests of the strains to the other antibiotics including penicillin G (10 µg), erytromycin (15 µg), clindamycin (15 µg), co-trimoxazole (trimethoprim/sulfamethoxazole), (1.25/23.75 µg), telithromycin (15 µg), and linezolid (30 µg) (Oxoid, Basingstoke, UK) were performed using the standard disk diffusion method. *S. aureus* ATCC 29213 and *S. aureus* ATCC 25923 standard strains were used as controls.

## Results

Sixty-seven percent of MRSA strains were isolated from skin and soft tissue infections, 12% from blood, and the rest were isolated from other specimens. Seventy-one percent of MRCNS strains were isolated from blood; the rest were isolated from other samples. In this study, no linezolid, quinupristin/dalfopristin or daptomycin resistant strains among both MRSA and MRCNS strains were found, and no intermediate susceptibility to vancomycin (VISA) or resistant (VRSA) strains among the MRSA strains was found. Two MRCNS strains were found to be resistant to teicoplanin (MIC 256 µg/mL), and one was found to be intermediate-susceptible (MIC 16 µg/mL). One (2%, isolated from an abscess) MRSA strain and two (3%, isolated from blood and drainage) MRCNS strains were found to be resistant to tigecycline (MIC 1 µg/mL). Telithromycin resistance was found to be 33% in the MRSA strains, and 37% in the MRCNS strains. Nine of MRSA strains (18%) and 18 of MRCNS strains (30.5%) had inducible clindamycin resistance. $MIC_{50}$ and $MIC_{90}$ values for daptomycin, quinupristin/dalfopristin, tigecycline, and vancomycin and resistance rates to all antibiotics of the strains are shown in Table 1 and Table 2.

## Discussion

As a result of the growing resistance problem among bacteria and the serious infections caused by resistant bacteria, morbidity and mortality rates increase, hospital stays are prolonged, and costs rise. There has been an increase in the resistance of MRSA and MRCNS strains to antibiotics. Reports of resistance to glycopeptides first appeared in Japan [13] and the U.S [39]; other countries reported resistance to vancomycin or intermediate strains. These increasing rates of resistance demonstrate the need for new antibiotics [14,44]. In the last ten years, broad-spectrum antibiotics such as daptomycin, linezolid,

quinupristin/dalfopristin, telithromycin, and tigecycline, which have an effect on methicillin-resistant staphylococci have been developed; the work on a few new antibiotics continues.

Tigecycline is a tetracycline-derivative antibiotic that has a broad spectrum. Tigecycline prevents the entry of aminoacyl transfer RNA into ribosome in bacteria by binding to the A zone of the ribosomal 30S subunit. Thus, chain elongation in protein synthesis is blocked and bacterial growth stops due to the ending of protein synthesis [6,45]. The most important mechanism of resistance development is tetracycline resistance genes (*tet*) that enable the production of efflux pump proteins and ribosomal protection. Tigecycline overcomes this resistance mechanism because the efflux pumps are not able to eject glycylcyclines from the cell. Multidrug transport systems of some bacteria lead to a fourfold increase in MIC values but do not provide resistance to tigecycline [15]. However, a recent investigation has shown that overexpression of *mep*A, a novel multidrug and toxic compound extrusion (MATE) family efflux pump, may contribute to a decreased susceptibility to tigecycline in *S. aureus* [45]. In surveillance studies, no strains naturally resistant to glycylcycline were found among the clinical strains, but it was reported that the development of resistant bacteria may have occurred as a result of glycylcycline being used widely in the treatment [8]. Tigecycline is an effective antibiotic against both Gram-positive and Gram-negative microorganisms but is reported to be most effective against Gram-positive strains [9,34]. It has been reported that tigecycline was effective against Gram-positive and Gram-negative bacteria in the Tigecycline Evaluation and Surveillance Trial (TEST) study in 2009 [4]. Florescu *et al*. [10] showed that the rate of success of tigecycline therapy was similar to that of vancomycin in skin-soft tissue infections. In the current study, tigecycline resistance was exhibited by one of the MRSA strains and two of the MRCNS strains. Since tigecycline had not been used in the treatment of patients from whom the strains were isolated, the resistance could have been developed through a mechanism not related to antibiotic use; for example, by the MATE efflux pump family. It was striking to detect the 3.1% resistance rate to tigecycline in a multi-center study (n = 260) in Turkey [17]. Kaya *et al*. reported that the MIC of only one of 60 MRSA strains was over the sensitivity level [21]. Kandemir *et al*. reported that tigecycline may be an alternative to teicoplanin in experimental MRSA osteomyelitis [19]. Hope *et al*. reported that tigecycline was highly effective against MRSA and MRCNS strains that had been isolated from bacteremia [12].

In the TEST study, Brandon *et al*. found that all of the 3614 *S. aureus* strains isolated from child patients were susceptible to linezolid, vancomycin, and tigecycline. They noted that tigecycline and linezolid had high activity against the Gram-positive agents of child patients [47]. In the TEST 2004-2009 study, 41.3% of the *S. aureus* strains were MRSA, and the MRSA strains were found to be susceptible to linezolid at a rate of 100% and to tigecycline at a rate of 99.98%. Moreover, it was reported that tigecycline and linezolid continue to show good activity against Gram-positive isotones across the globe [48]. In a 2011 study that reviewed tigecycline activities in the North America, Europa, Latin America and Asia-Pacific regions, tigecycline showed a large spectrum and powerful activity against serious infections including multi-resistant organisms [49].

Recently, clinical resistance to tigecycline following treatment with tigecycline has been observed. It has been reported that long-term monotherapy carries a high risk for tigecycline resistance, often in the *Acinetobacter* spp. and *Enterobacteriaceae* family. Tigecycline resistance has been seen in the muti-resistant strains. In addition, it has been reported that the factors which decrease sensivity against tigecycline were RND-type transporters and other efflux pumps, and that tigecycline should be used in clinics carefully [50]. There have been two studies reporting that tigecycline-resistant staphylococcus strains were found. In one, among a total of 2610 species (Gram-positive and Gram-negative), one *S. haemolyticus* was found to be resistant to tigecycline [23]. In the other study, tigecycline resistance was detected in 1.8% of the 1989 community-acquired MRSA strains [27].

Telithromycin is the first member of the ketolide class of antibiotics. Ketolides inhibit protein synthesis by binding the peptidyl transferase region of the 50S subunit of bacteria ribosome. Two mechanisms play a role in resistance development to macrolides: macrolide, linkosamid, streptogramin b (MLSb) resistance and the pump mechanism, but telithromycin is not affected by inducible resistance because it has the keto group in third position instead of L-cladinose sugar in its structure [2]. It has been widely reported that telithromycin is effective in methicillin-sensitive *S. aureus* strains, though it is not effective in MRSA

strains [37]. In the current study, resistance to telithromycin was found at a rate of 33% of MRSA strains, which confirms this information. Sacha *et al*. found that 92.3% of all *S. aureus* strains were resistant to telithromycin [35]. Kaya *et al*. found that 21% of MRSA strains and 41% of MRCNS strains isolated from various clinial samples were resistant to telithromycin [22]. Telithromycin was specifically designed for the treatment of community-acquired respiratory tract infections. It has been reported that telithromycin is effective against *S. aureus* and coagulase negative staphylococci, but strains that have the MLSb resistance mechanism are also resistant to ketolides [42]. In this study, the relationship between MLSb and telithromycin resistance was consistent. In a PROTEKT (Prospective Resistant Organize Tracking and Epidemiology for Ketolide Telithromycin) study, susceptibility to telithromycin in MRSA strains was reported to vary by region. In this study, telithromycin susceptibility for MRSA was reported to be 3.92% in Asia, 32.92% in Europe, 71.43% in Australia, 25.33% in North America, 2.15% in Latin America, and 17.85% on average [5].

Linezolid is the sole oxazolidinone in clinical use today. Oxazolidinones, which are effective against Gram-positive bacteria and mycobacteria, are often ineffective on Gram-negative bacteria because they have endogenous efflux pumps [42]. Linezolid is different from other protein synthesis inhibitors in terms of the mechanism of action; it prevents the formation of the 70S beginning complex by binding to 50S subunits at the ribosomes [29]. Therefore, the development of *in vitro* resistance to linezolid is difficult. The single-nucleotide changes in the genes encoding 23S ribosomal RNA lead to the development of resistance to linezolid. Similar point mutations have been seen in resistant clinical strains [26]. Only one clinical strain of linezolid-resistant *S. aureus* has been reported in the literature [40]. In the present study, no resistance to linezolid was found in MRCNS or MRSA strains; likewise, no domestic studies have found linezolid resistance to methicillin-resistant staphylococci. In a study by *Kanan et al*. [18], all the Gram-positive cocci strains were susceptible to linezolid; the $MIC_{90}$ value for linezolid was 2 µg/mL for MRSA strains and 1 µg/mL for MRCNS strains.

Wunderink *et al*. (2012) found that linezolid had clinically higher success rates than vancomycin in the MRSA treatment of the patients with nosocomial pneumonia [20]. According to the results of the TEST surveillance study performed in eastern European countries between 2004 and 2010, all the MRSA strains were susceptible to linezolid and tigecycline; linezolid and vancomycin were effective against the Gram-positive pathogens [51].

Quinupristin/dalfopristin is the first injectable streptogramin combination that has been developed for clinical use in the United States. It contains quinupristin and dalfopristin in the ratio of 30:70. Streptogramins are synergistic bactericidal agents that inhibit protein synthesis in susceptible bacteria. They are mainly effective on Gram-positive bacteria [42]. Resistance to streptogramins can develop by mechanisms such as ribosomal target modification, enzymatic inactivation, and efflux pumps [30]. Yavuz *et al*. [43] found that of 100 MSSA and 100 MRSA strains, one MRSA strain isolated from the conjunctival swab was resistant to quinupristin/dalfopristin. In a multi-center study in Turkey (n = 260), it was reported that quinupristin/dalfopristin resistance had been detected in 5% of MRSA strains [17]. Sacha *et al*. (2008) and Tverdek *et al*. (2008) found no resistance to quinupristin/dalfopristin; it was the first alternative drug to vancomycin and was indicated as an alternative option for MRSA treatment [35,41]. Millan *et al*. (2004) found quinupristin/dalfopristin resistance in 2.5% of MRSA strains [28]. In the current study, quinupristin/dalfopristin-resistant strains were not found among MRSA and MRCNS strains.

Daptomycin is the first lipopeptide antibiotic obtained from *Streptomyces roseosporus* [1]. Daptomycin irreversibly binds to the cytoplasmic membrane of susceptible bacteria via calcium ion association, adding to the hydrophobic end of the molecule; this causes membrane depolarization, resulting in cell death without cell lysis. Similar to VISA strains, daptomycin may develop resistance by thickening the bacteria cell wall to form physical barriers or by other mechanisms [42]. Daptomycin received FDA approval for use in complicated skin-soft tissue infections in 2003, and for right-sided endocarditis and *S. aureus* bacteremia in 2006 [25,39,46,54]. Fowler *et al*.found that *S. aureus* is more beneficial for right-sided endocarditis and bacteremia than the standard therapy; FDA approval was granted based on this study [54]. Daptomycin was reported to be effective in the treatment of skin and subcutaneous infections and blood infections caused by MRSA in many studies [12,31,35]. In the present study, 67% of MRSA strains were isolated from skin

and soft tissue infections, and 12% were isolated from blood. Although vancomycin was considered to be the gold standard treatment of bacteraemia/infective endocarditis caused by MRSA, there are studies reporting treatment failure in vancomycin-susceptible strains. However, it has been reported that daptomycin is as effective as vancomycin in the treatment of bacteraemia/infective endocarditis caused by MRSA [11]. Moore *et al*. (2012) found that better therapy results are obtained with daptomycin compared to vancomycin in bacteremias caused by MRSA strains that had high MICs of vancomycin [53]. Dohmen *et al*. (2013) examined the use of daptomycin in patients with infective endocarditis (IE). Most of the patients with left-sided IE used daptomycin for staphylococcus infection treatment, and a high clinical achievement ratio was obtained (91% for right-sided IE, 76% for left-sided IE, 80% average). The clinical success in the patients who used daptomycin at a higher dosage than 8 mg/kg was determined as 90%. The treatment success ratio was 84% in the MSSA strains, and 81% in the MRSA strains [24]. In a multi-center study in Turkey (n = 260), it was reported that daptomycin resistance was detected in 0.4% of MRSA strains [17]. Only one study reported daptomycin resistance (MIC: 2 µg/mL) in MRSA strains outside Turkey [32]. In many studies, daptomycin has been indicated to be a good treatment option for especially serious and resistant Gram-positive bacteria infections [16,36]. In a study conducted in Canada, the sensitivity ratio in MRSA strains was found to be 100% for daptomycin and linezolid, and 99.8% for tigecycline [52]. In their study evaluating the MIC changes of vancomycin, linezolid, daptomycin, and oxacillin in the U.S. over a five-year period, Steinkraus *et al*. indicated that the MIC values for daptomycin showed a more significant reduction than the mean MIC values [38].

In this study, three teicoplanin-resistant and intermediate MRCNS strains were found; these strains were found to be susceptible to daptomycine, linezolid, and quinupristin/dalfopristin. This result showed that daptomycine is effective against microorganisms that are resistant to teicoplanin. Based on these results, daptomycine appears to be a good therapy option for infections caused by these bacteria. Similarly, in a study by Betriu *et al*. (2001), linezolid was found to be potentially useful in the treatment of infections caused by MRSA and for MRCNS strains that have decreased sensitivity to teicoplanin [3].

## Conclusions

In the current study, *in vitro* activity of linezolid was found to be similar to vancomycin in methicillin-resistant staphylococci. Resistance to tigecycline was detected in 2% of MRSA strains and 3% of MRCNS strains; this result has led to concerns that other resistant strains can be found in the near future. Although it has recently come into use, telithromycin has a high percentage of resistance and its use for methicillin-resistant staphylococcal strains should be limited. Daptomycin and quinupristin/dalfopristin were found to be effective against MRSA and MRCNS strains and were concluded to be a good choice in the treatment of methicillin-resistant staphylococci. Although glycopeptides are the gold standard therapy for treatment of MRSA infections, MRSA/MSSA strains with decreased susceptibility to glycopeptides have begun to emerge in the last few years. As even small changes in vancomycin MIC values may be clinically significant, when vancomycin MICs exceed the sensitivity limit, alternative treatments have been proposed to prevent possible treatment failure.

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