Determination of antimicrobial susceptibility patterns and inducible clindamycin resistance in Staphylococcus aureus strains recovered from southeastern Turkey

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Antibiotic susceptibility; Inducible clindamycin resistance; Staphylococcus aureus

Background: In this study, we determined the susceptibility patterns of Staphylococcus aureus strains to various antimicrobials and prevalence of inducible clindamycin resistance (ICR) in these isolates.

Methods: Two hundred and one S aureus strains, isolated from various clinical samples, were included in the study. Antibiotic susceptibilities were studied by disc diffusion method on the basis of the guidelines by the Clinical and Laboratory Standards Institute. The disc diffusion induction test (D test) was applied to determine ICR resistance among erythromycin-resistant S aureus isolates.

Results: Of the 201 S aureus strains, 101 (50.2%) were resistant to methicillin. All strains were susceptible to vancomycin, teicoplanin, quinupristin/dalfopristin, and linezolid. It was found that 54 (53.4%) methicillin-resistant S aureus (MRSA) strains were erythromycin resistant, and 40 (39.6%) of them showed constitutive clindamycin resistance. ICR was detected in seven (6.9%) MRSA strains. It was found that 13 (13.0%) methicillin-susceptible S aureus (MSSA) strains were erythromycin resistant. Constitutive clindamycin resistance was seen in one (1.0%) MSSA strain, and ICR was detected in 10 (10.0%) cases.

Conclusion: There was a high rate of methicillin resistance among S aureus strains in our hospital. However, no statistically significant difference of ICR was observed between MRSA and MSSA strains (p = 0.434) or between inpatients and outpatients (p = 0.804). It was concluded that ICR should be routinely evaluated in each S aureus case to avoid therapy failure among patients.

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Introduction

Methicillin resistance in staphylococci is an increasing problem in clinical practice because methicillin-resistant *S. aureus* (MRSA) strains are resistant to other antimicrobial agents and isolates, with reduced susceptibility and resistance to vancomycin have also emerged.\(^6,9\) Once such a strain is recognized to be the causative agent of an infection, it is of interest to determine which of the alternatives to vancomycin is suitable for therapy. In *in vitro* susceptibilities of MRSA strains, especially those from community-acquired infections, to clindamycin (CLI), erythromycin (ERY), quinolone antibiotics, tetracyclines, and trimethoprim-sulfamethoxazole have frequently been reported.\(^2,3\)

The macrolide-lincosamide-streptogramin B (MLSB) family of antibiotics is commonly used in the treatment of staphylococcal infections.\(^4\) However, this widespread use has led to an increase in the number of staphylococci strains resistant to MLSB antibiotics.\(^5,6\) Macrolide antibiotic resistance in *S. aureus* and coagulase-negative staphylococci may be because of an active efflux mechanism encoded by *msr A* (confering resistance to macrolides and Type B streptogramins only) or ribosomal target modification affecting macrolides, lincosamides, and Type B streptogramins (MLSB resistance). *erm* genes encode enzymes that confer inducible or constitutive resistance to MLS agents via methylation of the 23S ribosomal RNA, thereby reducing binding by MLS agents to the ribosome.\(^4,7\) *In vitro* susceptibility of *S. aureus* isolates with constitutive resistance are resistant to ERY and CLI, and isolates with inducible resistance are resistant to ERY but appear to be susceptible to CLI. *In vivo*, therapy with CLI may select for constitutive *erm* mutants,\(^8\) which may lead to clinical failure.\(^6,9\) Constitutive resistance can be readily detected, but inducible resistance is not detectable by routine antimicrobial susceptibility tests.\(^6\) According to the recommendation of the Clinical and Laboratory Standards Institute (CLSI), testing for inducible clindamycin resistance (ICR) in isolates of staphylococci should be subjected to the D-zone test.\(^10\)

In this study, we aimed to determine the susceptibility pattern of *S. aureus* strains to various antimicrobials. We also aimed to determine the incidence of MLSB resistance among *S. aureus* isolates from various clinical samples and detect ICR strains.

Materials and methods

Staphylococci were recovered from various clinical samples at the Microbiology Laboratory of Gaziantep University Hospital from January to November 2007. Duplicate isolates from the same patient were not included in the study. In total, 201 *S. aureus* isolates were obtained from clinical specimens, comprising 147 (73.1%) inpatient and 54 (26.9%) outpatient isolates. Of the 201 *S. aureus* strains, 52 (25.9%) were recovered from pus, 38 (18.9%) from blood, 28 (13.9%) from tracheal aspirates, 21 (10.4%) from urine, 19 (9.5%) from throat sample, 18 (9%) from sputum, and 25 (12.4%) from other samples. Distribution of *S. aureus* strains by origin of recovery is shown in Table 1.

Definitions of inpatient infections were set according to the Centers for Disease Control and Prevention,\(^11\) which defines a nosocomial infection as a localized or systemic condition that results from adverse reaction to the presence of an infectious agent not present or incubating at the time of admission to the hospital.

Strains were identified by conventional methods (colony morphology, Gram stain, catalase activity, slide and tube coagulate tests, and DNase test) and an automated identification system (VITEK 2; bioMerieux, St Louis, MO, USA).

For the investigation of methicillin resistance, cefoxitin discs (30 μg) and oxacillin discs (1 μg) were used. Their antimicrobial susceptibility tests were performed by disc diffusion method according to the suggestions of CLSI.\(^10\) The isolates were tested for susceptibility to chloramphenicol (30 μg), CLI (2 μg), ERY (15 μg), levofloxacin (5 μg), linezolid (30 μg), quinupristin-dalfopristin (15 μg), teicoplanin (30 μg), telithromycin (15 μg), trimethoprim-sulfamethoxazole (1.25/23.75 μg), and vancomycin (30 μg) (Oxoid, Basingstoke, UK). Quality control was performed with *S. aureus* strain ATCC 25923; inhibition zone diameters were in the ranges stipulated by the CLSI.\(^10\)

Isolates that were CLI susceptible and erythromycin resistant (ER-R) were tested for inducible resistance by the D test. A 0.5 McFarland-equivalent suspension of organisms was inoculated onto a Mueller-Hinton agar plate as described in the CLSI recommendations.\(^10\) CLI and ERY discs were placed 15–20 mm apart from center to center on Mueller-Hinton agar plates. Plates were analyzed after 18 hours incubation at 35°C. Interpretation of the inhibition zone diameters was as follows: If an isolate was ER-R and

### Table 1 Distribution of MRSA and MSSA strains according to their origin of recovery

<table>
<thead>
<tr>
<th>Specimens</th>
<th>MRSA Inpatient isolates</th>
<th>MRSA Outpatient isolates</th>
<th>MSSA Inpatient isolates</th>
<th>MSSA Outpatient isolates</th>
<th>Total, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pus</td>
<td>22</td>
<td>—</td>
<td>11</td>
<td>19</td>
<td>52 (25.9)</td>
</tr>
<tr>
<td>Blood</td>
<td>22</td>
<td>—</td>
<td>14</td>
<td>2</td>
<td>38 (18.9)</td>
</tr>
<tr>
<td>Tracheal aspirate</td>
<td>22</td>
<td>—</td>
<td>6</td>
<td>—</td>
<td>28 (13.9)</td>
</tr>
<tr>
<td>Urine</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>12</td>
<td>21 (10.4)</td>
</tr>
<tr>
<td>Throat sample</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>11</td>
<td>19 (9.5)</td>
</tr>
<tr>
<td>Sputum</td>
<td>8</td>
<td>1</td>
<td>7</td>
<td>2</td>
<td>18 (9)</td>
</tr>
<tr>
<td>Other samples</td>
<td>14</td>
<td>1</td>
<td>9</td>
<td>1</td>
<td>25 (12.4)</td>
</tr>
<tr>
<td>Total</td>
<td>94</td>
<td>7</td>
<td>53</td>
<td>47</td>
<td>201 (100)</td>
</tr>
</tbody>
</table>

*MRSA* = methicillin-resistant *Staphylococcus aureus*; *MSSA* = methicillin-susceptible *Staphylococcus aureus*.
CLI susceptible, with a D-shaped inhibition zone around the CLI disc, it was considered to be positive for inducible resistance (D test positive). If the isolate was ER-R and CLI susceptible, with both zones of inhibition showing a circular shape, the isolate was considered to be negative for inducible resistance (D test negative), but to have an active efflux pump. If the isolate was ER-R and CLI resistant, the isolate was considered to have the macrolide-lincosamide-streptogramin B constitutive (MLSBC) phenotype.4

Results

Of the 201 S aureus strains, 101 (50.2%) were resistant to methicillin (MRSA) and 100 (49.8%) were susceptible to methicillin (MSSA). The distribution of MSSA strains was as follows: in 53 of 147 inpatients (36.1%) and in 47 of 54 outpatients (87%). MRSA strains were obtained mostly from inpatients (n = 94 of 147; 63.9%).

All isolated S aureus strains were found susceptible to linezolid, quinupristin/dalfopristin, teicoplanin, and vancomycin. Rates of resistance in MRSA and MSSA to antimicrobial agents were chloramphenicol, 11% and 5%; CLI, 39.6% and 1%; ERY, 53.4% and 13%; levofloxacin, 52.5% and 1%; telithromycin, 39.6% and 0%; and trimethoprim-sulfamethoxazole, 10% and 1%, respectively. Antimicrobial susceptibility results of MRSA and MSSA from inpatients and outpatients are shown in Table 2. There was a statistically significant difference of MRSA presence between inpatients (63.9%) and outpatients (13%) (p = 0.000). MRSA strains were significantly more resistant to ERY (p = 0.000), telithromycin (p = 0.000), levofloxacin (p = 0.000), and trimethoprim-sulfamethoxazole (p = 0.005), when compared with MSSA strains.

It was found that 54 (53.4%) MRSA strains were ERY resistant and 40 (39.6%) of them showed constitutive CLI resistance. ICR was detected in seven (6.9%) MRSA strains. It was found that 13% of MSSA strains were ERY resistant. Constitutive CLI resistance was seen in 1% of MSSA strains, and ICR was detected in 10% of the cases (Table 3). There was a statistically significant difference of constitutive CLI resistance in MRSA strains when compared with MSSA strains (p = 0.000). However, no statistically significant difference of ICR was observed between MRSA and MSSA strains (p = 0.434) or between inpatients and outpatients (p = 0.804).

Discussion

S aureus is one of the important pathogens causing bacteremia and nosocomial infection. The multidrug resistance to most of the antibiotics used in infections caused by staphylococci is an increasing problem. The emergence of methicillin resistance among S aureus strains led to difficulties in the treatment of infections caused by these microorganisms.12 The very highest rates of methicillin resistance among S aureus isolates have been noted in developed countries, and especially in Western Pacific Regions, both in community-acquired and nosocomial infections.13

In our study, methicillin resistance of staphylococci was found to be 50.2%. MRSA prevalence was reported between 33% and 71.3% in several studies from our country.14–16 In West Asia, MRSA prevalence ranged from 12% to 49.4% in six different hospitals of Saudi Arabia and was reported to be 62.5% in Pakistan.17,18 In European countries, MRSA rates varied from 0.6% in Sweden to 40.2%–45% in Belgium, Greece, Ireland, Italy, the United Kingdom, and Israel.19,20 In the Mediterranean region, the highest overall proportions of MRSA were reported by Jordan, Egypt, and Cyprus, where more than 50% of the S aureus blood culture isolates were methicillin resistant.21 In a study performed in 17 different regions of Russia, methicillin resistance among S aureus strains was between 0% and 89.5%.22 The differences in the prevalence of MRSA in different countries emphasize the importance of local surveillance in generating relevant local resistance data that can guide empiric therapy.23

There was a statistically significant difference of MRSA presence between inpatients (63.9%) and outpatients (13%) (p = 0.000). Another study from Pakistan notified that 62.5% of staphylococci were detected as MRSA and most of them were recovered from hospitalized patients.18 Shrestha et al.24 reported that 44.9% of MRSA strains were

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Antibiotic susceptibility profiles of MRSA and MSSA isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotic</strong></td>
<td><strong>MRSA (n = 101)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Inpatient isolates (n = 94)</strong></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>S</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>55</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>45</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>34</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>55</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>83</td>
</tr>
</tbody>
</table>

I = Intermediate; MRSA = methicillin-resistant Staphylococcus aureus; MSSA = methicillin-susceptible Staphylococcus aureus; R = resistant; S = susceptible.
associated with nosocomial infections. A high occurrence of MRSA was expected in nosocomial infections as the organisms developed resistance in the closed environments of hospitals and health care facilities because of selection pressure and their convenience in spreading from patient to patient via the health care workers and instruments.

In our study, despite the high prevalence of MRSA and increased use of vancomycin and teicoplanin, there was no isolate with reduced susceptibility to glycopeptides, and all strains were found susceptible to vancomycin, teicoplanin, quinupristin/dalfopristin, and linezolid. Although the isolates in this study were tested in 2007 and no vancomycin and teicoplanin resistance was found, it should still be pointed out that disc diffusion test for vancomycin in staphylococci is no longer recommended by CLSI starting from 2009 and that the ability of teicoplanin disc diffusion test to differentiate resistant from susceptible strains is not known.

Quinupristin-dalfopristin showed excellent activity, equal to that of vancomycin, against all S aureus isolates. Although the bactericidal activity of quinupristin/dalfopristin could be compromised because of the high prevalence of ERY-resistant MRSA, it might provide a valuable option for the treatment of MRSA infections. In addition, all of the isolates were susceptible to the new agent linezolid although a few isolates of linezolid-resistant S aureus were reported elsewhere. Linezolid has limited activity against selected gram negatives and anaerobes; however, it is highly active against gram-positive bacteria, including resistant strains. Like quinupristin/dalfopristin, linezolid is active against MRSA.

In this study, it was observed that 10% and 11% of the MRSA strains were resistant to trimethoprim-sulfamethoxazole and chloramphenicol, respectively. Most of the MRSA isolates were resistant to multiple other antimicrobial agents. In general, elevated rates of multidrug resistance may emerge from diverse isolates of S aureus under antimicrobial pressure or as a result of widespread person-to-person transmission of multidrug resistant isolates.

In our study, although telithromycin resistance was detected in 40 (39.6%) MRSA strains, no resistance was detected in MSSA strains. In this study, telithromycin was found to be more effective than ERY against MRSA and MSSA strains. Although resistances to telithromycin and CLI were similar in MRSA and MSSA strains, telithromycin was found to be more effective than CLI because of the inducible resistance in CLI.

The increasing frequency of staphylococcal infections among patients and changing patterns in antimicrobial resistance have led to renewed interest in the use of CLI therapy to treat such infections. CLI is indicated for the treatment of soft tissue infections, pediatric infections caused by staphylococci, or for patients allergic to beta-lactam agents. It is a good alternative to the treatment of both MRSA and MSSA infections; however, therapeutic failures caused by inducible MLSB resistance are being reported more commonly.

In a study from Greece, the constitutive macrolide resistance phenotype predominated in S aureus strains (47% MRSA; 13% MSSA) and was followed by the inducible (15% MRSA; 20% MSSA) and the CLI-susceptible (5%) phenotypes. In Iran, 17 of 175 (9.7%) S aureus isolates showed ICR; 11 (64.7%) strains were MRSA and 6 (35.3%) isolates were MSSA. In our country, different resistance rates came from two different studies; in one of them, the constitutive CLI resistance was 40.9% in MRSA isolates and 6.3% in MSSA strains, and the inducible resistance phenotype level was 25.1% in MRSA isolates and 16.4% in MSSA isolates, whereas, in the second one, the constitutive CLI resistance was 43.7% in MRSA isolates and 0% in MSSA strains, and the inducible resistance phenotype level was 5.4% in MRSA isolates and 10.7% in MSSA isolates.

The incidence of MLSB resistance varies significantly by geographical region. In Europe, there is a high incidence (93%) of the constitutive phenotype in MRSA, whereas the inducible phenotype is predominant in methicillin-susceptible S aureus. In our study, MRSA strains showed 39.6% constitutive CLI resistance and 6.9% ICR, whereas MSSA strains showed 1% constitutive CLI resistance and 10% ICR. Thus, in MRSA isolates, the level of constitutive CLI resistance was higher than the level of inducible resistance. Schreckenberger et al. reported incidences of ICR to be between 7% and 12% for MRSA and between 19% and 20% for MSSA in two different hospitals. Likewise, in our study, inducible CLI-resistant strains were more prevalent in MSSA (10%) than in MRSA (6.9%). Nevertheless, this difference was statistically insignificant (p = 0.434).

Inducible CLI-resistant staphylococci show susceptible results in conventional susceptibility tests but can be converted to a constitutively resistant phenotype during CLI.

### Table 3 Susceptibility of Staphylococcus aureus strains to erythromycin and clindamycin

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>MRSA (%)</th>
<th>MSSA (%)</th>
<th>Total, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inpatient isolates (n = 94)</td>
<td>Outpatient isolates (n = 7)</td>
<td>Total, n (%)</td>
</tr>
<tr>
<td>ER-S, CL-S</td>
<td>45</td>
<td>2</td>
<td>47 (46.6)</td>
</tr>
<tr>
<td>ER-R, CL-R</td>
<td>39</td>
<td>1</td>
<td>40 (39.6)</td>
</tr>
<tr>
<td>ER-S, CL-R</td>
<td>39</td>
<td>1</td>
<td>39 (39.6)</td>
</tr>
<tr>
<td>ER-R, CL-S, D-</td>
<td>4</td>
<td>3</td>
<td>7 (6.9)</td>
</tr>
<tr>
<td>ER-R, CL-S, D+</td>
<td>6</td>
<td>1</td>
<td>7 (6.9)</td>
</tr>
<tr>
<td>Total n (%)</td>
<td>101 (50.2)</td>
<td>100 (49.8)</td>
<td>201</td>
</tr>
</tbody>
</table>

CL = clindamycin; D- = D test negative; D+ = D test positive; ER = erythromycin; MRSA = methicillin-resistant Staphylococcus aureus; MSSA = methicillin-susceptible Staphylococcus aureus; R = resistant; S = susceptible.
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