



Minimum Inhibitory Concentration of Linezolid, Teicoplanin and Vancomycin in Methicillin -Resistant Staphylococcus Aureus

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ABSTRACT

Background: Methicillin-resistant Staphylococcus aureus causes a wide range of serious infections in the hospital and community. The importance of these human pathogens, in addition to its ability in the creation of life-threatening infections, is also its potential for developing antimicrobial resistance. The aim of this study was to determine the minimum inhibitory concentration of Linezolid, Teicoplanin and Vancomycin in methicillin-resistant Staphylococcus aureus isolated from patients admitted to training hospitals of Urmia in 2015-2016.

Methods: In this cross-sectional study, 216 isolates of Staphylococcus aureus isolated from clinical samples (from intensive care unit, urology, pediatric and orthopedic ward), after diagnostic tests 114 isolates of Staphylococcus aureus were isolated. Verified isolates with Linezolid, Teicoplanin and Vancomycin E.Test tapes were investigated through microdilution method and based on CLSI standards.

Results: Of 114 Staphylococcus aureus isolates, 94 isolates (82.45%) were resistant to methicillin and 20 isolates (17.54%) were susceptible to methicillin as well as 88 isolates (93.6%) of methicillin-resistant Staphylococcus aureus were susceptible to all antibiotics and 6 isolates (6.4%) were resistant to all antibiotics. However, none of Staphylococcus aureus strains were not intermediate to all antibiotics.

Conclusion: Methicillin-resistant Staphylococcus aureus is increasingly on the rise. The results of these studies should be available to hospitals in order to be informed of the status of antibiotic resistance in various sectors to adopt basic measures for controlling and eradicating resistant and dangerous strains and preventing the entry of these strains to community by proper and effective planning.

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Introduction

Staphylococcus aureus is a gram-positive, immobile cocci and without spores with a diameter of 0.5 to 1.5 microns and can be found in the form of individual, pairs, three-dimensional irregular clusters like grapes and short chain. Staphylococcus aureus infections are the second most common hospital pathogen that Staphylococcus aureus is the most important type of them. The high intake and widespread use of Broad-spectrum antibiotics such as third-generation cephalosporin, macrolides and fluoroquinolones is the effective factor of resistance of Staphylococcus aureus to methicillin (1).

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As well as methicillin-resistant *Staphylococcus aureus* causes a wide range of serious infections in the hospital and society (2, 3) and in the terms of acquiring infection can be divided into two categories: a) Hospital-acquired-MRSA, b) Community-acquired-MRSA (4). The type of Community-acquired-MRSA has a potential ability to create several clinical cases that can be attributed to the skin and soft tissue infections such as acne, abscesses and folliculitis, while the type of Hospital-acquired-MRSA are related to the infection of circulatory and respiratory system, osteomyelitis and surgical wound (2). The importance of these human pathogens, in addition to the creation of life-threatening infections, it is also the potential ability for the development of antimicrobial resistance (5).

Phenotypic and genotypic methods such as specific chromogenic culture, the use of cefoxitin discs 30 µg and oxacillin 10 µg and the presence of *mecA* gene in these isolates with PCR can be used to identify MRSA (2, 4).

More than a hundred thousand cases of MRSA infections are reported mainly from health centers, but according to some studies estimate the number could reach one million annually. The increasing incidence of methicillin-resistant *Staphylococcus aureus* strains has complicated the treatment. Intermediate and resistant to Vancomycin in methicillin-resistant *Staphylococcus aureus* have been reported in different countries, even Iran, so that restrictions of methicillin-resistant *Staphylococcus aureus* treatment has caused now a new class of antibiotics for the treatment of *Staphylococcus aureus* with multiple resistance (6).

Linezolid influences on the big subunit of ribozyme and because of this effect, the protein synthesis in bacteria is prevented, so that it is used to treat the serious and dangerous infections caused by methicillin-resistant *Staphylococcus aureus*. The first clinical isolate of methicillin-resistant *Staphylococcus aureus* against linezolid was introduced in 2007 (7).

Estimates show that 170,000 infections in the health care sector of Europe cause more than 5000 deaths annually, over 1 million of additional hospitalization and approximately 380 million euro of additional cost (3), and 132000 cases of MRSA report annually from the hospitals of Germany that deaths caused by MRSA were more than HIV in 2005 (8). Therefore, due to the increase of *Staphylococcus aureus* antibiotic-resistant strains of bacteria, the aim of this study was to determine the minimal inhibiting concentration of Linezolid, Teicoplanin and Vancomycin in methicillin-resistant *Staphylococcus aureus* isolated from patients admitted to training hospitals of Urmia in 2015-2016.

Methods and Materials

The samples were collected during 6 months from the clinical and para-clinical training hospitals of Urmia from intensive care unit, urology, pediatric and orthopedic ward, and were transferred to the laboratory for isolation of methicillin-resistant *Staphylococcus aureus* and were identified on special inoculated culture using standard microbiological tests (Gram stain, culture, blood agar, catalase test and coagulase test). Coagulase-positive *Staphylococcus aureus* bacteria were performed other procedures that were detected by tests.

To detect methicillin-resistant isolates, as a phenotypic the proposed methods of Clinical and laboratory Standards institute (CLSI) was used. For this purpose, cefoxitin discs 30 µg and oxacillin 10 µg were used because oxacillin is stable compared to methicillin in the temperature of laboratory. While first the monotonous suspension of the culture of desired bacteria with equivalent to 0.05 McFarland was prepared and cultured using a sterile soap on the Mueller Hinton agar like grass and then two discs were spaced by 24 mm from each other on the mentioned plate and was placed on the plate for 24-18 hours at 37 ° C. After a mentioned period, the diameter of no-growth Halo around the discs using the ruler with mm unit was measured and the mentioned diameter related to oxacillin disc was less than 21 mm and related to cefoxitin was less than 13 mm, samples were resistant to Methicillin (MRSA).

The resistance of the samples of interest to Cefoxitin and oxacillin indicated the resistance to beta-lactam antibiotics such as penicillin, Methicillin and cephalosporin (9, 10). The minimum inhibitory concentration of the growth of MRSA isolates to three new antibiotics was determined using E-test. For this purpose, E-test tapes of Vancomycin, Linezolid and Teicoplanin purchased from the Liofilchem ® company were used. First the monotonous suspension of the culture of desired bacteria with equivalent to 0.05 McFarland was prepared and cultured on the Mueller Hinton agar. After placing the tape including a gradient of antibiotic concentration on the culture, it was kept for 24 hours at 37 ° c maintenance and MIC was considered as a number palced in the conjunction of no-growth Halo with E-Test tape (11). The data obtained from this were analyzed using SPSS software version 18 and descriptive statistics (frequency and percentage).

Results

From January 2015 to June 2016, a Total of 216 isolates of Gram-positive were collected from training hospitals of Urmia University of medical sciences and transported to the laboratory. After additional and standardized tests (gram stain, catalase test, coagulase test and antimicrobial susceptibility), identification of isolates was confirmed (Table 1).

Of 216 isolates, 114 (53%) belonged to the *Staphylococcus aureus* and 102 (47%) to the coagulase-negative *Staphylococci*.

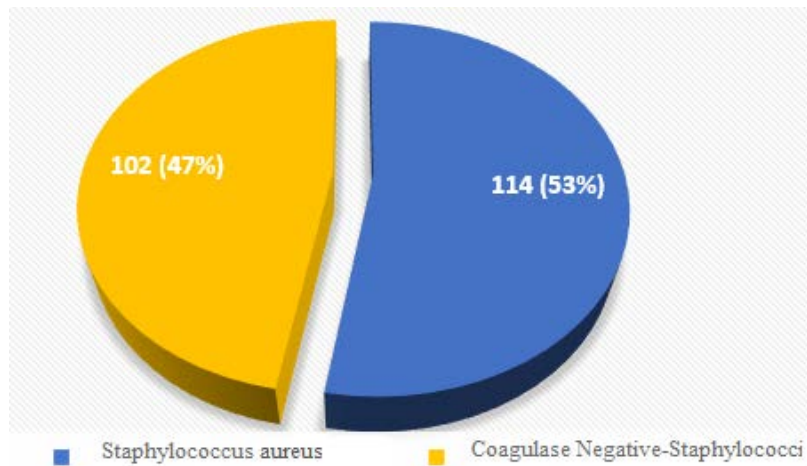


Figure 1.The frequency of studied *Staphylococcus aureus* isolates

Determining of resistance to methicillin in samples

After identification of *Staphylococcus aureus* isolates from samples transported to the laboratory, susceptibility test to two oxacillin and cefoxitin antibiotics for the detection of methicillin-resistant *Staphylococcus aureus* was performed. Of 114 *Staphylococcus aureus* isolates, 94 isolates (82.45%) were resistant to methicillin and 20 isolates of MRSA (17.54%) were susceptible to methicillin.

Determining of susceptibility to methicillin in samples

Finally after identification of methicillin-resistant *Staphylococcus aureus* isolates, susceptibility of these isolates to three antibiotics vancomycin, Teicoplanin and Linezolid were evaluated by E.test.

Table 1. The susceptibility of methicillin-resistant *Staphylococcus aureus* isolates to three antibiotics

| Minimum Inhibitory Concentration ($\mu\text{g/ml}$) | ≥ 0.38 | 0.5 | 0.75 | 1 | 1.5 | 2 | 3 | 4 | 6 |
|---|-------------|-----|------|----|-----|----|----|---|---|
| Vancomycin | 2 | 11 | 14 | 27 | 26 | 7 | 1 | - | - |
| Teicoplanin | 4 | 2 | 9 | 22 | 15 | 11 | 16 | 8 | 2 |
| Linezolid | 1 | 8 | 25 | 18 | 26 | 8 | 2 | - | - |

According to Table 1, the frequency of vancomycin MIC were as following: MIC: 0.5 $\mu\text{g/ml}$ = 12.5 %, MIC: 1 $\mu\text{g/ml}$ = 30.68 %, MIC: 1.5 $\mu\text{g/ml}$ = 29.5 %, MIC: 2 $\mu\text{g/ml}$ = 7.95 %, MIC: 3 $\mu\text{g/ml}$ = 1.13 %. The frequency of Teicoplanin MIC were as following: MIC: 0.5 $\mu\text{g/ml}$ = 2.24 %, MIC: 1 $\mu\text{g/ml}$ = 24.7 %, MIC: 1.5 $\mu\text{g/ml}$ = 16.85 %, MIC: 2 $\mu\text{g/ml}$ = 12.35 %, MIC: 3 $\mu\text{g/ml}$ = 18 %. The frequency of linezolid MIC were as following: MIC: 0.5 $\mu\text{g/ml}$ = 9.09 %, MIC: 1 $\mu\text{g/ml}$ = 20.45 %, MIC: 1.5 $\mu\text{g/ml}$ = 29.5 %, MIC: 2 $\mu\text{g/ml}$ = 9.09 % and MIC: 3 $\mu\text{g/ml}$ = 2.27 %.

The minimum inhibitory concentration (MIC) is the least dilution of antibiotics to prevent the growth of microbes. According to CLSI 2015 standard; minimum inhibitory concentration (MIC) for vancomycin in staphylococci aureus is $\leq 2\mu\text{g/ml}$, for Teicoplanin $\leq 8\mu\text{g/ml}$ and for linezolid $\leq 4\mu\text{g/ml}$.

Table 2. Minimum Inhibitory Concentration (MIC) for three antibiotics vancomycin, Teicoplanin and Linezolid in *Staphylococcus aureus* isolates according to the CLSI standard 2015.

| MIC ($\mu\text{g/ml}$) | Susceptible | Intermediate | Resistance |
|--------------------------|-------------|--------------|------------|
| Vancomycin | ≤ 2 | 4-8 | ≥ 16 |
| Teicoplanin | ≤ 8 | 16 | ≥ 32 |
| Linezolid | ≤ 4 | - | ≥ 8 |

According to Table 2, the minimum inhibitory concentration of *Staphylococcus aureus* isolates that were resistant and intermediate to vancomycin, were $16 \leq$ and 4-8, respectively, so that it was ≥ 32 and 16 for *Staphylococcus aureus* isolates which were resistant and intermediate to Teicoplanin as well as it was ≥ 8 for Linezolid.

Table 3. The results of antibiogram of *Staphylococcus aureus* isolates, based on the resistance to three antibiotics vancomycin, Teicoplanin and Linezolid

| MIC ($\mu\text{g/ml}$) | Suseptibale N (%) | Intermediate N (%) | Resistant N (%) |
|--------------------------|----------------------|-----------------------|--------------------|
| Vancomycin | 88 (93.6%) | - | 6 (6.4%) |
| Teicoplanin | 88 (93.6%) | - | 6 (6.4%) |
| Linezolid | 88 (93.6%) | - | 6 (6.4%) |

According to Table 5, 88 (93.6%) of *Staphylococcus aureus* isolates were susceptible to all three antibiotics and 6 isolates (6.4%) were resistant to all three antibiotics. However, none of *Staphylococcus aureus* strains were not intermediate to all three antibiotics.

Discussion

The widespread use of antibiotics has been associated with progressive enhancement of antibiotic resistance. Resistance factors often are associated with mobile genetic elements such as transposon or conjugative plasmids which can facilitate the gene transfer of resistance to other bacteria through horizontal gene transfer (12). Methicillin-Resistant *Staphylococcus aureus* can cause a range of serious infections in the hospital and the Community (2, 3). The importance of these human pathogens, in addition to the creation of life-threatening infections, it is also the potential ability for the development of antimicrobial resistance (5).

Vancomycin is one of the antibiotics which is the frequent in hospital environments, especially is used to treat the Methicillin-Resistant *Staphylococcus* and despite the few number of *Staphylococcus* that have resistant to Vancomycin have been reported very low, but the possibility of the presence of more resistant strains is very high in the near future (13). The most important cause of the creation of medium-strength and resistant strains is usually the presence of Methicillin-Resistant strains that were constantly faced with Vancomycin in the hospital because there is an indiscriminate consumption of Vancomycin (14).

In the study conducted by Sheetal et al. (15), 74% of isolated *Staphylococcus* were resistant and 26% were also susceptible to Methicillin, while Farajzadeh et al. (16), reported that 50% of isolated *Staphylococcus* were susceptible to Methicillin, but in our study its amount was 17.54% that was very low in comparison with other studies. It is also a study in the center of Iran (Arak) titled epidemiology of Methicillin-resistant *Staphylococcus aureus* strain which of 700 isolated *Staphylococcus*, 154 isolates (22%) were Methicillin-resistant that the results of Vancomycin E test indicated that contrary to the results of the present study, all strains are susceptible to Vancomycin (14).

In our study, 93.6 % of isolated *Staphylococcus* were susceptible to each of three types of antibiotics (Linezolid, Teicoplanin and Vancomycin) and 6.4 % were resistant to all three antibiotics. While none of the *Staphylococcus* strains were intermediate to all three antibiotics. In the study conducted by Sheetal et al. (15), 100 % of isolated *Staphylococcus* were susceptible to Linezolid, Teicoplanin and Vancomycin. In the study conducted by Chong et al. (17), 99.6% of the strains were susceptible to Vancomycin, and 0.4 % were also intermediate, while all strains (100%) were susceptible to Linezolid. As well as there are several other reports of strains with intermediate resistance in the United States, France, Brazil, South Korea and Iran, so that there are reports in the case of resistant strain mainly from the United States and India (14).

In the study of Ahmadi et al. (18), 14 % of *Staphylococcus* strains were resistant to Vancomycin while this percent in the present study was 6.4%. Also, in the study conducted by Iris et al. (19) 100% of *Staphylococcus* strains were susceptible to Vancomycin. In the study conducted by Wang et al. in 2005 (20), 100 % of *Staphylococcus* strains were susceptible to Vancomycin and Linezolid. In another survey in Korea, 53 out of 4483 Methicillin-Resistant *Staphylococcus* strains cases were resistant to Vancomycin, and none of them had intermediate resistance to Vancomycin (16, 21) that were consistent with the results of this study. In another study in training hospital of Ivory Coast, 38.7% from 45.4% of detected *Staphylococcus* were resistant to Methicillin which was more than our obtained results (22).

In the study of Bohlouli et al. in 2016 (23), the frequency of vancomycin MIC: 1.5 $\mu\text{g/ml}$ =24%, MIC: 2 $\mu\text{g/ml}$ =40% and MIC: 3 $\mu\text{g/ml}$ =18% was reported, while in our study the frequency of vancomycin MIC were 29.5%, 7.95% and 1.13, respectively. In the study of BanuSancak et al. (24), the frequency of vancomycin MIC: 1 $\mu\text{g/ml}$ =86%, MIC: 1.5 $\mu\text{g/ml}$ =28% and MIC: 2 $\mu\text{g/ml}$ =2% have been reported.

In terms of the frequency of Teicoplanin MIC in the study of Sheetal et al., in 2013(15), Teicoplanin MIC: 1 $\mu\text{g/ml}$ = 8 %, MIC: 1.5 $\mu\text{g/ml}$ = 8%, MIC: 2 $\mu\text{g/ml}$ = 32 %, MIC: 3 $\mu\text{g/ml}$ = 14% have been reported, while the frequency of Teicoplanin MIC : 1 $\mu\text{g/ml}$ = 24.7 %, MIC: 1.5 $\mu\text{g/ml}$ =16.85 %, MIC: 2 $\mu\text{g/ml}$ =12.35 % and MIC: 3 $\mu\text{g/ml}$ = 18 %.

Conclusion

The results of this study indicate a high level of resistance to Methicillin in isolated *Staphylococcus*. Hence the choice of the right antibiotic, continuous evaluation of resistance patterns as well as the treatment of infections caused by *Staphylococcus* have more importance. The study also shows that *Staphylococcus aureus* strains are very important on the distribution of the antibacterial resistance and the treatment of infections caused by them should be serious matter to reduce this process. The

results of these studies should be available to hospitals in order to be informed of the status of antibiotic resistance in various sectors to adopt basic measures for controlling and eradicating resistant and dangerous strains and preventing the entry of these strains to community by proper and effective planning.

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Conflict of Interest

The authors declared that there is no conflict of interest in this study.

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