GLYCOPEPTIDES AND LINEZOLID MIC CHANGES IN STAPHYLOCOCCUS AUREUS AND COAGULASE NEGATIVE STAPHYLOCOCCI ISOLATES FROM 2008-2011

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ABSTRACT

***Aims**: Glycopeptides and linezolid are the antimicrobial agents used for the treatment of methicillin resistant Staphylococcus aureus (MRSA) and methicillin resistant Coagulase negative Staphylococci (MRCoNS) infections. It is emerging concern about an increase minimum inhibitor concentration (MIC) of vacomycin among S. aureus strains. In this study, we aimed to analyse the trends in MICs of vancomycin, teicoplanin and linezolid over 4 years (2008-2011) period.*

***Materials and methods**: Identification and MICs of the isolates were tested in Vitek2 Compaktand Phoenix (Becton Dickinson, Diagnostic Systems, USA) automated systems. MIC50 (defined as the minimum concentration at which 50% of the isolates were inhibited), MIC90 (defined as the minimum concentration at which 90% of the isolates were inhibited) and mean MICs were evaluated. All calculations were performed for each year.*

***Results and conclusion**: No vancomycin, teicoplanin and linezolid resistant isolates were detected. The decreased in the mean MIC of vancomycin in S. aureus isolates over 4 years, was found significant. The increased, in the mean MIC of vancomycin in CoNS isolates among 2008-2009, was significant. Otherwise, the decrease in the mean MIC of teicoplanin and linezolid in S. aureus isolates, was significant among 2009-2010.*

***Key words**: S. aureus, vancomycin, teicoplanin, linezolid, MIC.*

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Introduction

Staphylococcus aureus is an important pathogen both in hospital and community-acquired infections in worldwide[(1)]. The mortality of S. aureus bacteremia, before the penicillin,was 80%. After the introduction of penicillin in 1940s, prognosis of patients with staphylococcal infections improved dramatically but, in 1942, first penicillin resistant isolate was determined. Methicillin is an semisynthetic penicillinase-resistant antimicrobial and was introduced in 1961, however methicillin resistant isolates were rapidly spread in both hospital and community.Methicillin resistant *S. aureus* (MRSA) is an important clinical problem due to multidrug resistance patterns of MRSA isolates[(2,3)].

In the recent studies, it has been determined that 60% of the *S. aureus* were isolated from intensive care units[(4)].

Glycopeptides are effective agents preferred in the treatment of MRSA infections[(4)].However in 1990s glycopeptides resistant and heteroresistant isolates were reported[(5,6,7,8)].

In recent years new antistaphylococcal antibiotics such as linezolid, the first oxazolidinone, were introduced as a therapeutic option in thetreatment of MRSA infections[(9)].

Glycopeptide resistant or intermediate isolates are rare among *S. aureus* clinical samples, but it is an emerging concern that vancomycin therapy failed in patients, with vancomycin MICs at the high end of the Clinical Laboratory and Standarts Institute (CLSI) susceptibility range[(10)].

In this study we aimed to investigate changes in MICs of vancomycin, teicoplanin and linezolid.

Material and method

The *S. aureus* and CoNS isolates included in this study, were obtained from specimens submitted to OndokuzMayıs University, Faculty of Medicine, Medical Microbiology Laboratory from January 2008 to December 2011. The identification of samples and determinations of the MICs were performed in Vitek2 Compact (Biomeriux, France) and Phoenix (Becton Dickinson, Diagnostic Systems, USA) automated systems. The results were interpreted according to the CLSI guidelines, MIC50, MIC90 and mean MICs were evaluated and all calculations were performed for each year in the study (Table 1)[11]. MIC trends, over 4 years, were assessed statistically using independent two sample T-test(p<0,005).

Antimicrobial		S	I	R
Vancomycin	*S. aureus*	≤2	4-8	≥16
	CoNS	≤4	8-16	≥32
Teicoplanin		≤8	16	≥32
Linezolid		≤4	-	≥8

Table 1: CLSI MIC values of vancomycin, teicoplanin and linezolid for S. aureus and CoNS.

Results

A total of 1518 *S. aureus* and 7041 CoNS isolates were collected from 2008 through 2011 and included in this study.

Penicillin and oxacillin resistance, in *S. aureus* and CoNS isolates, were determined as 98.1%, 30.2% and 96.2% and 76.3% respectively. Mean MIC, MIC50 and MIC90 of vancomycin, teicoplanin and linezolid for *S. aureus* and CoNSwere displayed in Table 2. The decrease in the mean MIC of vancomycin in *S. aureus* isolates, over 4 years,was found significant. The decrease in the mean MIC of teicoplanin and linezolid, in *S. aureus* isolates, was significant among 2009-2010; also the increase in the mean MIC of vancomycin in CoNS isolates among 2008-2009 was significant. The decrease in the mean MIC of teicoplanin among CoNS was significant between 2008 and 2010. The increase in the mean MIC of linezolid was significant after 2008 for CoNS.Mean MIC trends for *S. aureus* and CoNS were displayed in Figure 1 and Figure 2, respectively.

Antimicrobial	Year	Mean MIC	MIC50	MIC90
		S.aureus/CoNS	S.aureus/CoNS	S.aureus/CoNS
Vancomycin	2008	1.11 /1.25	1-Jan	2-Feb
	2009	1.06/1.32	1-Jan	2-Jan
	2010	1.03/1.14	1-Jan	2-Jan
	2011	1.01/1.07	1-Jan	1-Jan
Teicoplanin	2008	1.74/2.31	1-Jan	4-Apr
	2009	1.9/2.49	1-Jan	8-Apr
	2010	1.57/2.65	2-Jan	8-Apr
	2011	1.73/2.52	2-Jan	8-Apr
Linezolid	2008	1.74/1.75	2-Feb	2-Feb
	2009	1.9/1.74	2-Feb	2-Feb
	2010	1.57/1.78	2-Feb	2-Feb
	2011	1.73/1.29	2-Feb	2-Feb

Table 2: S. aureus and CoNS MIC(mg/L) statistics 2008-2011.

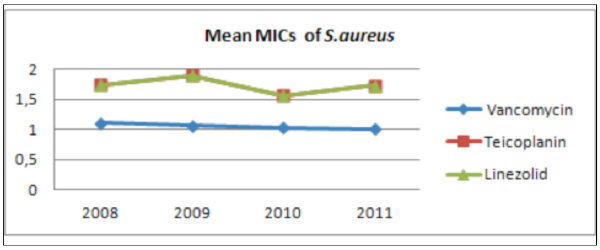

Fig. 1: Mean MICs distribution of S. aureus isolates among years.

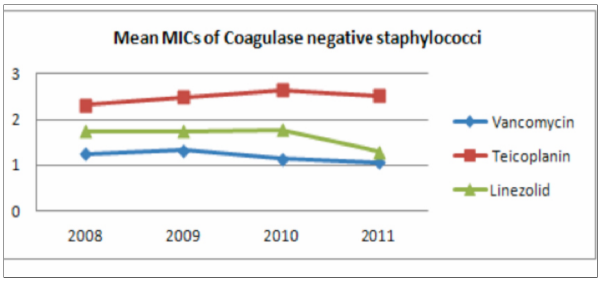

Fig. 2: Mean MICs distribution of coagulase negative staphylococci among years.

Discussion

MRSA is an increasing problem in hospital-acquired infections[12]. The cost of MRSA infections is higher than MSSA infections the higher cost of MRSA infections likely due to increased length of stay, delay in diagnosis, isolation procedures and ICU stay[13]. It is an emerging problem that therapeutic agents for the treatment of MRSA infections are limited. Glycopeptides and linezolid are highly recommended options for MRSA infections[12,14].

Vancomycin has been associated with some side effects as "red man sendrom", ototoxicity, neutropenia, fever, phlebitis, nephrotoxicity and thrombocytopenia. Sometimes these are the limitations for the vancomycin as a choice of MRSA infections[15]. Linezolid has bacteriostatic activity against bacteria and has potential bone marrow toxicity and neuropathy during longterm administration[16]. These are the some limitations of these drugs. *S. aureus* isolates with reduced susceptibility to vancomycin have been reported from several studies and these isolates have been accountable for the failure of treatment[17,18,19]. Therefore, Steinkraus et al[12] suggested close observation of vancomycin susceptibility trends and they suggested that it was necessary to examine the MIC statistic reports. There are two forms of *S. aureus* resistance to vancomycin. One of these mechanisms is the changes in peptidoglycan biosynthesis. And the second form of vancomycin resistance has occurred from the conjugation of vanA operon from vancomycin-resistant Enterococcus strains[3].

In our study, we analyzed the mean MIC, MIC50 and MIC90 of staphylococci isolates over 4 year period. We found there was no marked changes in MIC50 and MIC90 of the isolates. However, the analysis of the mean MIC changes among years, pointed out a significant decrease in the mean MIC of vancomycin in S. aureus. Despite the decreased mean MIC of vancomycin in S. aureus, we found that mean MIC vancomycin in CoNS isolates have significantly increased in 2008 and 2009.

Steinkraus et al.[12] analyzed *S. aureus* isolates over 5 year period and used E-test method for the determination of MIC. They reported increased MICs for vancomycin and linezolid. Golan et al.[20] reported 1.6 fold increase in geometric mean MIC of vancomycin over 4 year period. They mentioned that major increase in vancomycin MICs detected with isolates increasing from ≤0.5 to>0.5 mg/L. Wang et al.[21] evaluated 6603 clinical isolates of *S. aureus* over 5 year period and reported a statistically significant increase in the percentage of *S. aureus* isolates with a MIC of 1 mg/L (19.9% in 2000 and 70.4% in 2004)[14]. However, Rhee et al.[22] reported that they did not determine any change in *S. aureus* vancomycin MICs from 1994 to 1999. In Turkey, resistance to vancomycin, teicoplanin and linezolid was not detected[23,24,25,26,27].

Celikbilek et al.[28] investigated MIC50 and MIC90 in MRSA and they were determined MIC50 and MIC90 values were as 0.75 and 1.5 μg/ml for vancomycin, 2 and 3 μg/ml for teicoplanin, 0.38 and 0.5 μg/ml for linezolid. In a study from Europe, MIC50/MIC90 values were determined as; for vancomycin 1/2, for teicoplanin 1/2 and for linezolid 2/2[2].

Linezolid is an oxazolidinone that used for the treatment of MRSA infections[9]. Linezolid resistant *S. aureus* samples have been reported from hospital structure but it is still rare[29]. Linezolid resistance is not common in both MRSA and CoNS clinical isolates. The resistance mechanisms for linezolid are; mutation in the drug target site, rRNA of the large ribosomal subunit and acquisition of tarnsferable resistance gene cfr that modify a specific rRNA and mutations in rpID and rpIC genes which encode ribosomal proteins[30]. Golan et al.[20] reported a significant increased MRSA linezolid MICs from 2002 to 2005. They detected increase in the percentages of isolates with MICs of 4 and 8 mg/L. Steinkraus et al.[12,11] reported an increased in linezolid geometric mean. They detected that MIC changes occured especially with a decrease in MICs ≤ 0.5 mg/dl. In this study we detected significant increase mean MIC values of linezolid in *S. aureus* isolates in years 2009 and 2010. In a study from our country, Arslan et al.[25] determined MIC50 and MIC90 values for linezolid as 0.5 and 1, respectively.

In conclusion, it is necessary to observe MIC trends in *S. aureus* and CoNS for the appropriate treatments. And further investigations need for evaluation of MICs and treatment outcomes in healthcare structure.

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