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Antibiotic resistance patterns of methicillin-resistant coagulase negative staphylococci isolated from blood cultures at a university hospital in Turkey

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ABSTRACT

Aims: Recent reports indicate that many coagulase-negative staphylococci (CoNS) strains are resistant to most antimicrobials used against staphylococcal infections. This study was aimed to determine the species distribution of the CoNS isolates in Lokman Hekim Ankara Hospital and determine their antimicrobial resistance characteristics.
Methodology and results: The study was conducted at Lokman Hekim University Ankara Hospital between February 2020 and August 2021. The 154 blood cultures included in the study were incubated in the BACTEC FX40 automated blood culture device. Identification and antimicrobial susceptibility tests of the samples with positive catalase tests were performed with the BD Phoenix Automated Microbiology Sensitivity System. The statistical significance level was accepted as $p<0.05$. Nineteen different types of methicillin-resistant coagulase-negative staphylococci (MRCoNS) isolated from different age groups were identified. Vancomycin resistance was observed in 20 samples (13%). Trimethoprim-sulfamethoxazole (TMP-SMX) resistance was seen in 44 of 152 samples (28.6%), linezolid resistance in 15 of 143 samples (10.5%) and daptomycin resistance in 16 of 146 blood samples (11%).
Conclusion, significance and impact of study: In our investigation, there has been a striking rise in the prevalence of vancomycin, TMP-SMX, linezolid and daptomycin resistance among infections with the MRCoNS. Identifying and classifying multidrug resistance on MRCoNS requires reliable epidemiological data to be collected and compared between healthcare facilities in different countries. The research finding reported in this paper will contribute to the determination of alternative antibiotics for treating MRCoNS.

Keywords: Antibiotic, coagulase negative staphylococci, identification, methicillin resistance

INTRODUCTION

Staphylococci are important bacteria that colonize as the normal flora of the skin and mucous membranes. Different species of *Staphylococcus* are responsible for a variety of infections. *Staphylococcus aureus* is an opportunistic pathogen that can cause a variety of self-limiting to life-threatening diseases in humans. It is one of the most common causes of skin, soft tissue and nosocomial infection (Fridkin *et al.*, 2005). Coagulase-negative staphylococci (CoNS) have been considered contaminant bacteria for many years because they are found in the normal flora of the skin and mucosa. The importance of circulatory system infections has increased due to the increase in the use of central venous catheters in hospitalized patients. Adhesion of CoNS causes severe infections in various prosthetic and peritoneal dialysis catheters, orthopedic implants, prosthetic heart valves, supra-pubic catheters, joint prostheses, cerebrospinal shunts, invasive vascular catheters and urinary catheters. Recently, the rapid resistance of bacteria to various antibiotics has become a serious problem for clinicians (García-Vázquez *et al.*, 2013; Karakullukçu *et al.*, 2017; Park *et al.*, 2021). In this regard, up-to-date resistance information is needed for bacteria responsible for emerging infections that threaten human health, like infections caused by CoNS.

In a short time after the development of antibiotics, unconscious and unnecessary use of them caused rapid progress in resistance to antibiotics. The most critical problem of failure in treating staphylococcal infections is methicillin resistance. Methicillin resistance in staphylococci varies from country to country and even from region to region. In studies conducted in Turkey and abroad, it has been reported that methicillin resistance in CoNS is 40% to 71% (Khorshed and Özbal, 2012).

Recently, most CoNS strains have been resistant to antimicrobials used against staphylococcal infections. The spread of multidrug-resistant CoNS strains has increased with the use of antibiotics in hospitals, which creates a reservoir for antimicrobial-resistant strains. In a study conducted in Ethiopia, it was stated that methicillin

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resistance increased in CoNS and the prevalence of methicillin-resistant coagulase-negative staphylococci (MRCoNS) was relatively lower than that of MR *S. aureus* (MRSA) (Deyno *et al.*, 2018).

This may be due to the rare occurrence of CoNS infection compared to *S. aureus*, resulting in reduced antimicrobial exposure. However, it has been noted that CoNS continually evolves from commensal staphylococci to invasive pathogens and then into resistant strains, possibly acquiring resistant genes from *S. aureus* (Dilnessa and Bitew, 2016; Deyno *et al.*, 2018).

Methicillin-resistant staphylococci are clinically significant because they are resistant to all other beta-lactam antibiotics such as penicillin, cephalosporins and beta-lactam-beta-lactamase inhibitor combinations. Glycopeptides are among the antibiotics that can be used safely to treat infections caused by methicillin-resistant staphylococci. These staphylococci are generally resistant to erythromycin, clindamycin, chloramphenicol, tetracyclines, trimethoprim sulfamethoxazole (TMP-SMX), quinolones and aminoglycosides. Therefore, difficulties are encountered in the treatment and the use of glycopeptide antibiotics becomes compulsory (Asante *et al.*, 2021).

MATERIALS AND METHODS

Patients and specimen collection

The study was carried out at Lokman Hekim University Ankara Hospital between February 2020-August 2021. Two thousand one hundred and seventy-two (2172) blood cultures sent from different clinics were analyzed in the Microbiology Laboratory of LHU Ankara Hospital. One hundred and fifty-four MRCoNS isolated from 2172 blood cultures were included in this study. Demographic information about the patients, such as age and gender, were obtained from the hospital records. The study was performed following the Declaration of Helsinki for experiments involving humans and the study protocol was approved by the Research Ethics Committee of Lokman Hekim University (Decision No: 2020/008).

Microbiological methods

The patient was included in the study when the same bacteria were isolated in blood culture samples taken from both veins or one vein and one intravenous catheter of the respective patient. Only the first strain of patients with multiple growths in the selected bacteria was included in the study. Blood cultures were incubated in the BACTEC FX40 automated blood culture device for up to seven days. From the bottles that gave a growth signal, the passage was made into 5% Sheep Blood Agar and Eosin Methylene Blue Agar media. The cultured media were incubated at 37 °C for 18-24 h. After incubation, the catalase test was performed on the plates with colony appearance, staining properties and microscopic appearance compatible with staphylococci.

Identification and antimicrobial susceptibility tests

Identification and antimicrobial susceptibility tests of the samples with positive catalase tests were performed with the BD Phoenix Automated Microbiology Sensitivity System in accordance with the working protocol of the device recommended by the company and CLSI criteria. The system can identify bacteria and yeast at the genus and species level with the chromogenic and fluorogenic substrates it contains. The BD Phoenix Sensitivity System includes an oxidation-reduction indicator, turbidometric growth detection, full panel antimicrobial concentrations and typing system. As a result of these systems working as a whole, fast, accurate and reliable antimicrobial susceptibility results were provided. A total of 23 antibiotics (amikacin, amoxicillin, ampicillin, ampicillin/sulbactam, cefoxitin, ceftazidime, ciprofloxacin, clindamycin, daptomycin, erythromycin, fosfomycin, fusidic acid, gentamicin, gentamicin syenergi, levofloxacin, linezolid, methicillin, oxacillin, penicillin, teicoplanin, tetracycline, TMP-SMX and vancomycin) susceptibility test results were evaluated. The study was focused on vancomycin, TMP-SMX, daptomycin and linezolid because they are the antibiotics of choice in methicillin-resistant bacteria. The antibiotic resistance values obtained were evaluated in three classes: susceptible, intermediate and resistant.

Statistical analysis

The Mantel-Haenszel chi-square test was performed to determine whether there was a statistically significant difference in resistance to the four antibiotics. The Gamma test was used to determine whether there was a significant linear by linear association between the groups. The statistical significance level was accepted as $p<0.05$.

RESULTS AND DISCUSSION

Samples taken from male and female patients were included in the analysis (n=154); 5% were under the age of 3, 22% were between the ages of 3-65 and 73% were over the age of 65 (Figure 1). The mean age value for all samples was 69.50 years old, with a range of 97. In isolated MRCoNS samples (n=154), no significant difference was detected between the resistance developed against vancomycin, TMP-SMX, daptomycin and linezolid antibiotics. There was also no significant correlation between mentioned antibiotic resistance and the sex or age of the patient's samples included into study cohort (data not shown). Nineteen different types of MRCoNS isolated from different age groups were identified. Among the MRCoNS isolates, 51 (33.3%) were *S. epidermidis*, 21 (13.7%) were *S. haemolyticus*; 33 (21.5%) were defined as *S. hominis*, 16 (10.4%) as *S. capitis* and the rest belong to other sepsis with lower incidence.

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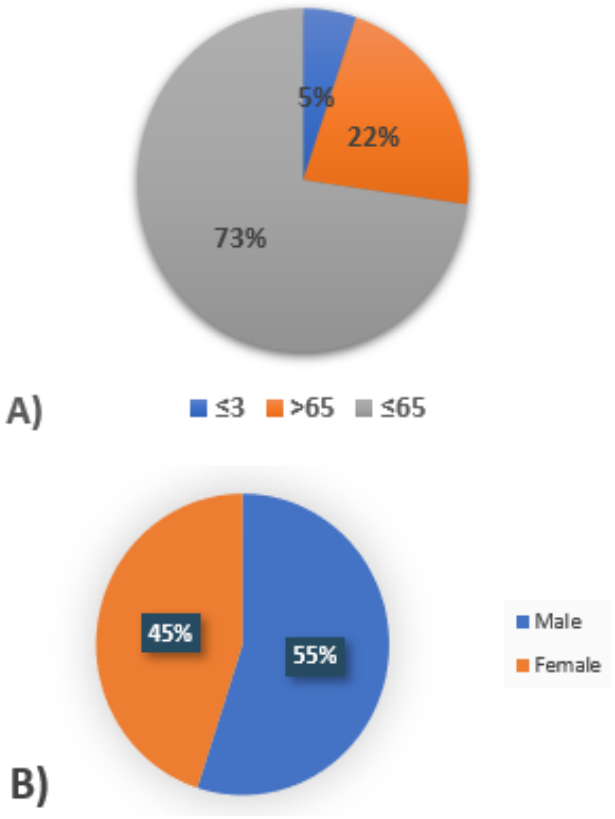

Figure 1: Distribution of samples by age groups (A) and by sex (B). In the isolated MRCoNS samples (n=154), there was no significant difference between the gender or age groups of the patients and the resistance to vancomycin, TMP-SMX, daptomycin and linezolid.

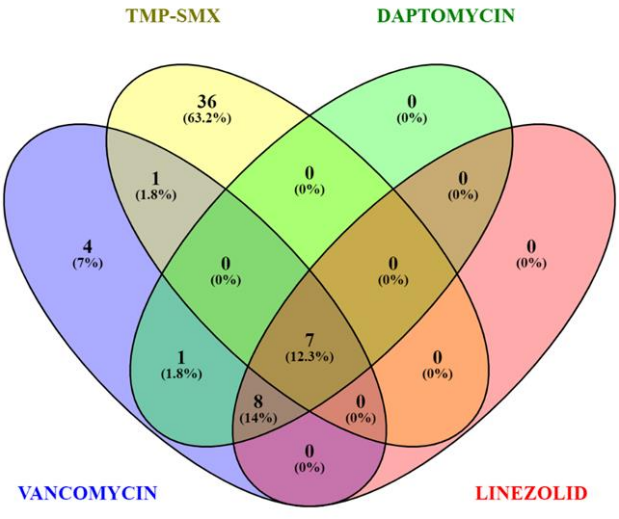

Figure 2: Venn diagram of susceptibility of samples to TMP-SMX, vancomycin, daptomycin and linezolid.

Other studies in Turkey reported that the rate of *S. epidermidis* isolates from clinical specimens is between 36-49%. This rate for other CoNS common strain isolates were *S. hominis* (42%) and *S. haemolyticus* (9%), respectively (Yiğit *et al*., 2008; Güzel-Tunçcan *et al.*, 2010; Çiftçi *et al.*, 2016). The CoNS types found in our study were compatible with studies conducted in Turkey.

Table 1 shows the valid and missing sample sizes for vancomycin, TMP-SMX, daptomycin and linezolid. With regard to each of these four antibiotics, sensitive, intermediate and resistant sample percents are presented in Table 2. Seven samples obtained from patients were found to be resistant to all four antibiotics (Figure 2).

A total of 133 samples were susceptible to vancomycin, 1 sample was found to be intermediate and 20 samples (13%) were found resistant. The resistance percent regard to TMP-SMX, daptomycin and linezolid were 28.6%, 11% and 10.5%, respectively (Table 2).

Since the number of intermediate samples to vancomycin was minimal, intermediate and susceptible groups were combined with increasing the power of the test. No statistically significant linear trend was observed in TMP-SMX scores as the vancomycin score increased (p=0.053 > α=0.05) (Table 3).

In the comparison of vancomycin and daptomycin, a statistically significant increase was observed in daptomycin scores as vancomycin increased (p < α=0.05). In this group, it was determined that there was a very strong positive (G=1) statistically significant relationship between the two variables (p<0.05) (Table 4).

In the comparison of vancomycin and linezolid groups, as shown in Table 5, a statistically significant increase is observed in linezolid scores as the vancomycin score increases (p < α=0.05). There was a positive, very strong G=1 statistically significant relationship between the two variables (p<0.05).

As TMP-SMX score increases, a statistically significant increase is observed in daptomycin scores p=0.031 < α=0.05. There is a positive moderate G=0.483 statistically significant relationship between the two variables, p=0.025 < 0.05 (Table 6).

As shown in Table 7, as TMP-SMX score increases, a statistically significant increase is observed in linezolid scores p=0.027 < α=0.05. There is a positive moderate G=0.502 statistically significant relationship between the two variables, p=0.025 < 0.05.

In the comparison of daptomycin and linezolid groups, as shown in Table 8, as the daptomycin score increased, a statistically significant increase was observed in linezolid scores p < α=0.05. There is a positive, very strong G=1 statistically significant relationship between the two variables, p<0.05.

Figure 3 shows the number of susceptible, intermediate and resistant samples obtained against vancomycin, TMP-SMX, daptomycin and linezolid, and the distribution of male and female patients.

Analysis (MH chi-square) between resistance to antibiotics and gender showed no statistical relationship (result not shown).

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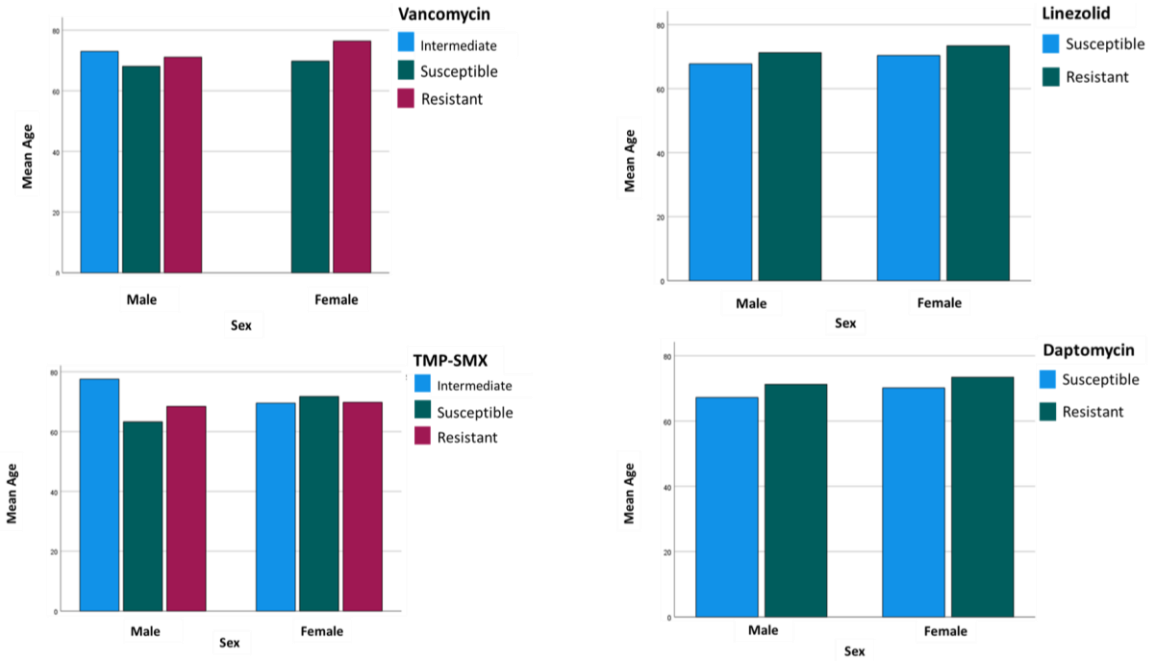

Figure 3: The number of susceptible, intermediate and resistant samples obtained against vancomycin, TMP-SMX, daptomycin and linezolid, and the distribution of male and female patients.

Table 1: The valid and missing sample sizes for vancomycin, TMP-SMX, daptomycin and linezolid.

		Vancomycin	TMP-SMX	Daptomycin	Linezolid
N	Valid	154	152	146	143
	Missing	0	2	8	11

Table 2: Frequency of vancomycin, TMP-SMX, daptomycin and linezolid in the sample cohort.

Vancomycin		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Susceptible	133	86.4	86.4	87.0
	Intermediate	1	0.6	0.6	0.6
	Resistant	20	13.0	13.0	100.0
	Total	154	100.0	100.0	
TMP-SMX		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Susceptible	73	47.4	48.0	71.1
	Intermediate	35	22.7	23.0	23.0
	Resistant	44	28.6	28.9	100.0
	Total	152	98.7	100.0	
Missing	System	2	1.3		
	Total	154	100.0		
Daptomycin		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Susceptible	130	84.4	89.0	89.0
	Resistant	16	10.4	11.0	100.0
	Total	146	94.8	100.0	
Missing	System	8	5.2		
	Total	154	100.0		
Linezolid		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Susceptible	128	83.1	89.5	89.5
	Resistant	15	9.7	10.5	100.0
	Total	143	92.9	100.0	
Missing	System	11	7.1		
	Total	154	100.0		

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Table 3: Vancomycin- TMP-SMX crosstabulation.

		TMP-SMX			Total
		Intermediate	Susceptible	Resistant	
Vancomycin	Intermediate	1	0	0	1
	Susceptible	33	62	36	131
	Resistant	1	11	8	20
Total		35	73	44	152

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	4.455[a]	2	0.108
Likelihood Ratio	5.676	2	0.059
Linear-by-Linear Association	3.748	1	0.053
N of Valid Cases	152		

a. 1 cells (16.7%) has expected count of less than 5. The minimum expected count is 4.61.

Table 4: Vancomycin- daptomycin crosstabulation.

		Daptomycin		Total
		Susceptible	Resistant	
Vancomycin	Intermediate	1	0	1
	Susceptible	125	0	125
	Resistant	4	16	20
Total		130	16	146

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	113.206[a]	1	0.000		
Continuity Correction[b]	105.156	1	0.000		
Likelihood Ratio	80.915	1	0.000		
Fisher's Exact Test				0.000	0.000
Linear-by-Linear Association	112.431	1	0.000		
N of Valid Cases	146				

a. 1 cells (25.0%) has expected count of less than 5. The minimum expected count is 2.19.
b. Computed only for a 2 × 2 table

Table 5: Vancomycin- linezolid crosstabulation.

		Linezolid		Total
		Susceptible	Resistant	
Vancomycin	Intermediate	1	0	1
	Susceptible	122	0	122
	Resistant	5	15	20
Total		128	15	143

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	103.061[a]	1	0.000		
Continuity Correction[b]	95.227	1	0.000		
Likelihood Ratio	73.519	1	0.000		
Fisher's Exact Test				0.000	0.000
Linear-by-Linear Association	102.340	1	0.000		
N of Valid Cases	143				

a. 1 cells (25.0%) has an expected count of less than 5. The minimum expected count is 2.10.
b. Computed only for a 2 × 2 table

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Table 6: TMP-SMX- daptomycin crosstabulation.

		Daptomycin		Total
		Susceptible	Resistant	
TMP-SMX	Intermediate	34	1	35
	Susceptible	64	8	72
	Resistant	30	7	37
Total		128	16	144
		Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square		4.698[a]	2	0.095
Likelihood Ratio		5.257	2	0.072
Linear-by-Linear Association		4.664	1	0.031
N of Valid Cases		144		

a. 2 cells (33.3%) have an expected count of less than 5. The minimum expected count is 3.89.

Table 7: TMP-SMX- linezolid crosstabulation.

		Linezolid		Total
		Susceptible	Resistant	
TMP-SMX	Intermediate	34	1	35
	Susceptible	62	7	69
	Resistant	30	7	37
Total		126	15	141
		Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square		4.916[a]	2	0.086
Likelihood Ratio		5.291	2	0.071
Linear-by-Linear Association		4.860	1	0.027
N of Valid Cases		141		

a. 2 cells (33.3%) have an expected count of less than 5. The minimum expected count is 3.72.

Table 8: Daptomycin- linezolid crosstabulation.

		Linezolid		Total	
		Susceptible	Resistant		
Daptomycin	Susceptible	127	0	127	
	Resistant	1	15	16	
Total		128	15	143	
	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	133.015[a]	1	0.000		
Continuity Correction[b]	123.218	1	0.000		
Likelihood Ratio	88.531	1	0.000		
Fisher's Exact Test				0.000	0.000
Linear-by-Linear Association	132.085				
N of Valid Cases	143				

a. 1 cells (25.0%) has an expected count of less than 5. The minimum expected count is 1.68.
b. Computed only for a 2 × 2 table

Staphylococcus gallinarum was detected in 4 (50%) of the samples with vancomycin and TMP-SMX resistance. At the same time, resistance formation against daptomycin and linezolid was detected in these samples. Species with vancomycin resistance were identified as *S. equorm*, *S. gallinarum*, *S. hominis*, *S. schleiferi*, *S. xylosus*, *S. capitis*, *S. carnosus*, *S. haemolyticus* and *S. lentus*.

Six (30%) *S. gallinarum* species were detected in 20 vancomycin-resistant samples, and it was determined as the species with the highest vancomycin resistance. Vancomycin resistance was found in four (20%) of 20 samples in *S. hominis*, which is one of the frequently isolated species. Although *S. epidermidis* was the most frequently isolated species, all strains were susceptible to vancomycin.

Bloodstream infections and catheter-related infections, of which CoNS are the leading causes, are important causes of morbidity and mortality despite antibacterial and supportive treatments. Therefore, early diagnosis and appropriate treatment are important (Pedroso *et al.*, 2018). As a result of intensive antibiotic use, especially in

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the hospital environment, MRCoNS are isolated as infectious agents. The unexpected increase in infections due to CoNS and their resistance to antibiotics has led to an increase in studies on typing these bacteria and determining their antibiotic susceptibility (Asante *et al.*, 2021).

Resistance to methicillin in staphylococci is one of the most important causes of failure in treating infections. Considering the multiple antibiotic resistance seen in methicillin-resistant staphylococci, first of all, methicillin-resistant staphylococci must be identified quickly and accurately to select the right antibiotic (Marincola *et al.*, 2021).

Glycopeptides are the first-line agents used to treat various infections caused by methicillin-resistant staphylococci. Vancomycin obtained from *Streptomyces orientalis* inhibits the transpeptidation step by binding to the D-alanyl-D-alanine end of peptidoglycan, a cell wall component and inhibits cell wall synthesis (Michels *et al.*, 2021).

The emergence of CoNS with decreased vancomycin susceptibility, the increase in the prevalence of glycopeptide-intermediate *S. epidermidis* (GISE) and the emergence of rifampin and gentamicin resistance in MR *S. epidermidis* (MRSE) strains have limited therapeutic options and the need for alternative bactericidal agents has increased (De La Mària *et al.*, 2015). In our study, vancomycin resistance was determined as 13% and TMP-SMX resistance was determined as 28.6% in CoNS strains. Previous European studies of glycopeptide resistance in CoNS and the European Glycopeptide Susceptibility Survey have shown an incidence rate ranging from 3% to 19%. In a prospective study conducted in Italy, it was stated that 4% of total CoNS isolates were resistant to glycopeptides, and an incidence rate of 8% was found in patients in the intensive care unit (Tacconelli *et al.*, 2001). In a study including 236 CoNS strains in Turkey, the rate of methicillin resistance was found to be 82%. While no resistance was found to vancomycin, daptomycin and linezolid, 95% resistance was found to penicillin and 20% to TMP-SMX (Çiftçi *et al.*, 2016).

TMP-SMX is an ancient antibiotic used against *S. aureus.* Trimethoprim is the main active ingredient and its combination is highly synergistic. It can be used as an additional option against MRSA due to its low cost, acceptable toxicity profile, both oral and intravenous administration and bactericidal activity. In addition, vancomycin is active against intracellular phagocytized MRSA and has higher clearance rates than vancomycin (Goldberg *et al.*, 2010). TMP-SMX is recommended as an appropriate treatment option due to the increasing number of hospital-acquired and community-acquired MRSA infections and the emergence of vancomycin resistance (Paul *et al.*, 2015; John, 2020).

In a study comparing vancomycin and TMP-SMX, high-dose TMP-SMX therapy was administered to MRSA patients and no superiority was achieved over vancomycin in the treatment of severe MRSA infections with increasing the dose (Paul *et al.*, 2015). In recent studies from Africa, it has been stated that *S. aureus* develops widespread resistance to TMP-SMX (Bowen *et al.*, 2017). In the study of Goldberg *et al.* (2010), the efficacy of vancomycin and TMP-SMX were evaluated, and it was shown that TMP-SMX had equal efficacy with vancomycin in the treatment of hospital-acquired pneumonia caused by MRSA. However, in a different study, it was reported that vancomycin had superior efficacy and safety than TMP-SMX in the treatment of staphylococcal pneumonia (Yayan *et al.*, 2015).

In our research, 8 (40%) of 20 MRCoNS strains with vancomycin resistance were also found to have TMP-SMX resistance. In 7 of 8 samples that developed vancomycin and TMP-SMX resistance, resistance also developed to daptomycin and linezolid. When the species showing this multi-resistance were examined, it was observed that 4 of 7 samples were *S. gallinarum*. *Staphylococcus gallinarum* is a pathogen that was first isolated from the skin of a chicken and is rarely seen to cause infections in humans (Tibra *et al.*, 2010). This suggests that being a zoonotic-origin species may be effective in becoming resistant. In our study, 36 samples (23%) were found to be vancomycin sensitive and TMP-SMX resistant. It was determined that 17 of these samples were *S. epidermidis* and 8 of them were *S. haemolyticus.* In a study conducted in Spain, *S. epidermidis* was reported as the most common type in the epidemiology of CoNS-induced infective endocarditis and methicillin resistance in 52% of the patients. When vancomycin MICs of 2.0 µg/mL were common in these patients, *S. epidermidis* isolates were found in almost all cases and did not increase over time (De La Mària *et al.*, 2015). Infections caused by *S. epidermidis* are clinically significant in hospitalized patients. Methicillin resistance is common in CoNS strains, with 81% being multidrug-resistant (Mendes *et al.*, 2012). Severe bacteremia has also been associated with CoNS infection and biofilm formation. Some *S. epidermidis* clones (CC2) have been found to show particularly high rates of multidrug resistance (May *et al.*, 2014). In a study conducted in the neonatal intensive care unit of a hospital in Brazil, it was reported that methicillin-resistant *S. epidermidis* isolates had a decreased susceptibility to vancomycin, which complicates the treatment of critically ill patients (Peixoto *et al.*, 2020).

In a study conducted in a hospital in Brazil, *S. haemolyticus* was the most resistant species to antimicrobials in bloodstream infections, followed by *S. epidermidis, S. hominis* and *S. warneri*. The isolated strains showed a multidrug resistance profile, while 93.1% of them were resistant to oxacillin; linezolid, teicoplanin, and vancomycin 1.7%; and 46.5% were found to be resistant to TMP-SMX (Pedroso *et al.*, 2018). *Staphylococcus haemolyticus* frequently colonizes the skin and mucous membranes of hospitalized patients and serves as a reservoir for antibiotic-resistance genes. Also, methicillin resistance rates are much higher than in *S. aureus*. It has also been reported that these strains have decreased susceptibility to glycopeptides and linezolid (Manoharan *et al.*, 2020).

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In a study conducted in Germany, resistance to vancomycin and linezolid was not found in patients with pneumonia caused by MRSA (Yayan *et al.*, 2015). New agents, including linezolid, daptomycin and tigecycline, have been developed as alternatives to glycopeptides against multiple resistant strains (Lourtet-Hascoët *et al.*, 2018). An Egyptian study indicated that vancomycin and linezoid exhibited the highest *in vitro* activity against all *S.* species and this activity was unaffected by methicillin resistance or biofilm-forming ability (Hashem *et al.*, 2017). Elsahn *et al.* (2010) showed that both MRSA and MRCoNS isolates were susceptible to vancomycin and linezolid. Gündoğuş *et al.* (2019) in Turkey found that MRSA strains had no resistance to vancomycin and linezolid. In our study, daptomycin resistance was found to be 11% and linezolid resistance was 10.5% among MRCoNS.

Daptomycin is a natural cyclic lipopeptide produced by *Streptomyces roseosporus*. It is used as a good option in the treatment of bacteremia and endocarditis caused by CoNS. In particular, daptomycin penetrates rapidly through the thick biofilm formed by *S. epidermidis*. Therefore, it is reported that it should be considered a leading treatment option in catheter-related bloodstream infections with a high probability of biofilm formation (Maraolo *et al.*, 2021). In a study comparing the efficacy of vancomycin and daptomycin, it was stated that clinical failure was less and better tolerated than vancomycin with the use of daptomycin in the treatment of patients with MRSA infection (Maraolo *et al.*, 2021). In our study, it was observed that there was a significant increase in daptomycin resistance with the increase in vancomycin resistance.

Linezolid is a bacteriostatic antibiotic that inhibits protein synthesis. The most widely used is oxazolidinone. Linezolid is reported as an option that should be considered, especially in the treatment of VRE infections. In a study conducted in Izmir, Turkey, linezolid [resistance rates respectively; 0-2% (17/830)] and glycopeptides [resistance rates, respectively; 0-9.7% (43/442)] are the most effective antimicrobials against many of staphylococcal and enterococcal species (Müderris *et al.*, 2019). Furthermore, only limited data are available to recommend its use as first-line therapy in CoNS. However, there have been significant increases in data on linezolid use in the recent past (Kramer *et al.*, 2019; Matrat *et al.*, 2020). In an extensive study of the feasibility of early-stage oral therapy in endocarditis, linezolid was mainly used in combination with other antibiotics. However, careless handling of linezolid has led to the emergence of linezolid-resistant strains, particularly linezolid-resistant *S. epidermidis* strains. CoNS have a higher and easier ability to acquire and develop linezolid resistance factors after drug exposure. The incidence of linezolid resistance in CoNS is currently higher than in *S. aureus.* It is believed that resistance to linezolid first appeared in CoNS and was later passed on to *S. aureus* (Michels *et al.*, 2021). Resistance to daptomycin and linezolid, which is preferred in cases where vancomycin resistance develops, creates the need for new antibiotics. In cases where vancomycin resistance develops, resistance to daptomycin and linezolid, which is preferred, creates a worrying situation with the loss of efficacy of antibiotics.

CONCLUSION

The emergence of resistance to multiple antimicrobial agents in pathogenic bacteria has become a public health threat due to the scarcity of antimicrobials that effectively treat infections caused by these pathogens. Recent studies show that there is an increase in MRCoNS infections with rising COVID-19. MRSA is among the most frequent causative agents of pulmonary infection in patients with COVID-19 (Chandran *et al.*, 2021; Bassetti *et al.*, 2022). This might be due to immune compromisation, immune-related pathways and gene dysregulation in COVID-19 patients (Türk *et al.*, 2020; Malkan *et al.*, 2021; Türk *et al.*, 2021). The resistance to CoNS health problems is constantly growing, and it is necessary to identify and classify multidrug-resistant bacteria so that reliable epidemiological data can be collected and compared between healthcare institutions and organizations in different countries. Therefore, precise definitions are needed.

The irrational use of antibiotics in hospitals and the continued use of over-the-counter antibiotics in some countries exacerbate this problem. Therefore, it is essential to maintain active systemic surveillance of these infections. This study includes up-to-date information about the antibiotic susceptibility profiles of MRCoNS isolates from Ankara Hospital, Turkey.

The results show that multi-antibiotic resistance is becoming a major problem in MRCoNS infections. The increase in vancomycin, TMP-SMX, linezolid and daptomycin resistance used in MRCoNS infections in this study is remarkable. The reported research findings will contribute to a better understanding of emerging resistance to MRCoNS.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

REFERENCES

Asante, J., Hetsa, B. A., Amoako, D. G., Abia, A. L. K., Bester, L. A. and Essack, S. Y. (2021). Multidrug-resistant coagulase-negative staphylococci isolated from bloodstream in the uMgungundlovu District of KwaZulu-Natal Province in South Africa: Emerging pathogens. *Antibiotics* **10(2), 198.**

 ISSN (print): 1823-8262, ISSN (online): 2231-7538

Bassetti, M., Magnasco, L., Vena, A., Portunato, F. and Giacobbe, D. R. (2022). Methicillin-resistant *Staphylococcus aureus* lung infection in coronavirus disease 2019: How common? *Current Opinion in Infectious Diseases* **35(2), 149-162.**

Bowen, A. C., Carapetis, J. R., Currie, B. J., Fowler, V., Chambers, H. F. and Tong, S. Y. C. (2017). Sulfamethoxazole-trimethoprim (cotrimoxazole) for skin and soft tissue infections including impetigo, cellulitis, and abscess. *Open Forum Infectious Diseases* **4(4), ofx232.**

Chandran, S., Avari, M., Cherian, B. P. and Suarez, C. (2021). COVID-19-associated *Staphylococcus aureus* cavitating pneumonia. *BMJ Case Reports* **14(6), e243726.**

Çiftçi, N., Türkdağı, H., Demircan, A. and Tuncer, İ. (2016). Identification and antibiotic resistance rates of coagulase-negative staphylococci isolated from blood cultures. *Ankem Journal* **30(1), 7-11.**

de la Mària, C. G., Cervera, C., Pericàs, J. M., Castañeda, X., Armero, Y., Soy, D., Almela, M., Ninot, S., Falces, C., Mestres, C. A., Gatell, J. M., Moreno, A., Marco, F., Miró, J. M. and Hospital Clinic Endocarditis Study Group. (2015). Epidemiology and prognosis of coagulase-negative staphylococcal endocarditis: impact of vancomycin minimum inhibitory concentration. *PLoS ONE,* **10(5), e0125818.**

Deyno, S., Fekadu, S. and Seyfe, S. (2018). Prevalence and antimicrobial resistance of coagulase negative staphylococci clinical isolates from Ethiopia: A meta-analysis. *BMC Microbiology* **18, 43.**

Dilnessa, T. and Bitew, A. (2016). Prevalence and antimicrobial susceptibility pattern of methicillin resistant *Staphylococcus aureus* isolated from clinical samples at Yekatit 12 Hospital Medical College, Addis Ababa, Ethiopia. *BMC Infectious Diseases* **9(16), 398.**

Elsahn, A. F., Yildiz, E. H., Jungkind, D. L., Abdalla, Y. F., Erdurmus, M., Cremona, F. A., Rapuano, C. J., Hammersmith, K. M. and Cohen, E. J. (2010). *In vitro* susceptibility patterns of methicillin-resistant *Staphylococcus aureus* and coagulase-negative *Staphylococcus* corneal isolates to antibiotics. *Cornea* **29(10), 1131-1135.**

Fridkin, S. K., Hageman, J. C., Morrison, M., Sanza, L. T., Como-Sabetti, K., Jernigan, J. A., Harriman, K., Harrison, L. H., Lynfield, R. and Farley, M. M. (2005). Methicillin-resistant *Staphylococcus aureus* disease in three communities. *The New England Journal of Medicine* **352(14), 1436-1444.**

García-Vázquez, E., Fernández-Rufete, A., Hernández-Torres, A., Canteras, M., Ruiz, J. and Gómez, J. (2013). When is coagulase-negative *Staphylococcus* bacteraemia clinically significant? *Scandinavian Journal of Infectious Diseases* **45(9), 664-671.**

Goldberg, E., Paul, M., Talker, O., Samra, Z., Raskin, M., Hazzan, R., Leibovici, L. and Bishara, J. (2010). Co-trimoxazole versus vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* bacteraemia: A retrospective cohort study. *Journal of Antimicrobial Chemotherapy* **65(8), 1779-1783.**

Gündoğuş, N., Gül, K., Dal, T. and Akpolat, N. (2019). Methicillin-resistant *Staphylococcus* strains isolated from adult intensive care units with E-test MIC values of different antibiotic research. *Dicle Medical Journal* **46(1), 51-64.**

Güzel-Tunçcan, O., Tozlu-Keten, D., Dizbay, M. and Şenol, E. (2010). Febril nötropenik hastalardan kateterle ilişkili kan dolaşımı infeksiyonu etkeni olarak izole edilen koagülaz-negatif stafilokok türlerinin teikoplanine duyarlılıkları. *Klimik Dergisi* **23(2), 44-47.**

Hashem, A. A., El Fadeal, N. M. A. and Shehata, A. S. (2017). *In vitro* activities of vancomycin and linezolid against biofilm-producing methicillin-resistant staphylococci species isolated from catheter-related bloodstream infections from an Egyptian tertiary hospital. *Journal of Medical Microbiology* **66, 744-752.**

John, J. (2020). The treatment of resistant staphylococcal infections. *F1000Research* **9, F1000 Faculty Rev-150.**

Karakullukçu, A., Kuşkucu M. A., Ergin, S., Aygün, G., Midilli, K. and Küçükbasmaci, Ö. (2017). Determination of clinical significance of coagulase-negative staphylococci in blood cultures. *Diagnostic Microbiology and Infectious Disease* **87(3), 291-294.**

Khorshed, A. and Özbal, Y. (2012). Kan kültürlerinde izole edilen koagülaz negatif stafilokokların tiplendirilmesi ve antibiyotik duyarlılıklarının araştırılması. *Sağlık Bilimleri Dergisi* **21(3), 153-163.**

Kramer, T. S., Schwab, F., Behnke, M., Hansen, S., Gastmeier, P. and Aghdassi, S. J. S. (2019). Linezolid use in German acute care hospitals: Results from two consecutive national point prevalence surveys. *Antimicrobial Resistance and Infection Control* **8, 159.**

Lourtet-Hascoët, J., Félicé, M. P., Bicart-See, A., Bouige, A., Giordano, G. and Bonnet, E. (2018). Species and antimicrobial susceptibility testing of coagulase-negative staphylococci in periprosthetic joint infections. *Epidemiology and Infection* **146(14), 1771-1776.**

Malkan, U. Y., Türk, S., Türk, C., Temirci, E. S., Koker, I. and Haznedaroğlu, İ. C. (2021). Interferon-gene family slterations following the SARS-Cov infection in sssociation with iron metabolism and lymphoid biology. *Uhod-Uluslararasi Hematoloji-Onkoloji Dergisi* **31(2), 67-78.**

Manoharan, M., Sistla, S. and Ray, P. (2020). Prevalence and molecular determinants of antimicrobial resistance in clinical isolates of *Staphylococcus haemolyticus* from India. *Microbial Drug Resistance* **27(4), 501-508.**

Maraolo, A. E., Giaccone, A., Gentile, I., Saracino, A. and Bavaro, D. F. (2021). Daptomycin versus vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* bloodstream infection with or without endocarditis: A systematic review and meta-analysis. *Antibiotics* **10(8), 1014.**

Marincola, G., Liong, O., Schoen, C., Abouelfetouh, A., Hamdy, A., Wencker, F. D. R., Marciniak, T., Becker, K., Köck, R. and Ziebuhr, W. (2021). Antimicrobial resistance profiles of coagulase-negative staphylococci in community-based healthy individuals in Germany. *Frontiers in Public Health* **9, 684456.**

Matrat, L., Plaisant, F., Barreto, C., Claris, O. and Butin, M. (2020). Increasing use of linezolid in a tertiary NICU during a 10-year period: Reasons and concerns for the future. *Antimicrobial Resistance and Infection Control* **9(1), 156.**

May, L., Klein, E. Y., Rothman, R. E. and Laxminarayan, R. (2014). Trends in antibiotic resistance in coagulase-negative staphylococci in the United States, 1999 to 2012. *Antimicrobial Agents and Chemotherapy* **58(3), 1404-1409.**

Mendes, R. E., Deshpande, L. M., Costello, A. J. and Farrell, D. J. (2012). Molecular epidemiology of *Staphylococcus epidermidis* clinical isolates from U.S. hospitals. *Antimicrobial Agents and Chemotherapy* **56(9), 4656-4661.**

Michels, R., Last, K., Becker, S. L. and Papan, C. (2021). Update on coagulase-negative staphylococci - What the clinician should know. *Microorganisms* **9(4), 830.**

Müderris, T., Yurtsever, S. G., Baran, N., Özdemir, R., Er, H., Güngör, S., Gökmen, A. A. and Kaya, S. (2019). Microorganisms isolated from blood cultures and the change of their antimicrobial susceptibility patterns in the last five years. *Turk Hijyen ve Deneysel Biyoloji Dergisi* **76(3), 231-242.**

Park, H., Park, S. B., Kim, J. and Kim, S. (2021). Distribution of coagulase-negative staphylococci and antibiotic resistance. *Biomedical Science Letters* **27(2), 45-50.**

Paul, M., Bishara, J., Yahav, D., Goldberg, E., Neuberger, A., Ghanem-Zoubi, N., Dickstein, Y., Nseir, W., Dan, M. and Leibovici, L. (2015). Trimethoprim-sulfamethoxazole versus vancomycin for severe infections caused by meticillin resistant *Staphylococcus aureus*: Randomised controlled trial. *BMJ* **350, h2219.**

Pedroso, S., Sandes, S., Filho, R., Nunes, A. C., Serufo, J. C., Farias, L. M., Carvalho, M., Bomfim, M. and Santos, S. G. (2018). Coagulase-negative staphylococci Isolated from human bloodstream infections showed multidrug resistance profile. *Microbial Drug Resistance* **24(5), 635-647.**

Peixoto, P. B., Massinhani, F. H., Dos Santos, K. R. N., Chamon, R. C., Silva, R. B., Correa, F. E. L., Oliveira, C. and Oliveira, A. G. (2020). Methicillin-resistant *Staphylococcus epidermidis* isolates with reduced vancomycin susceptibility from bloodstream infections in a neonatal intensive care unit. *Journal of Medical Microbiology* **69(1), 41-45.**

Tacconelli, E., Tumbarello, M., Donati K. G., Bettio, M., Spanu, T., Leone, F., Sechi, L. A., Zanetti, S., Fadda, G. and Cauda, R. (2001). Glycopeptide resistance among coagulase-negative staphylococci that cause bacteremia: Epidemiological and clinical findings from a case-control study. *Clinical Infectious Diseases* **33(10), 1628-1635.**

Tibra, N. K., Jalali, S., Reddy, A. K., Narayanan, R. and Agarwal, R. (2010). Traumatic endophthalmitis caused by *Staphylococcus gallinarum*. *Journal of Medical Microbiology* **59(Pt 3), 365-366.**

Turk, C., Turk, S., Malkan, U. Y. and Haznedaroglu, I. C. (2020). Three critical clinicobiological phases of the human SARS-associated coronavirus infections. *European Review for Medical and Pharmacological Sciences* **24(16), 8606-8620.**

Türk, S., Türk, C., Malkan, Ü. Y., Temirci, E. S., Peker, M. Ç. and Haznedaroğlu, İ. C. (2021). Current community transmission and future perspectives on the COVID-19 process. *Turkish Journal of Medical Sciences* **51(3), 1001-1011.**

Yayan, J., Ghebremedhin, B. and Rasche, K. (2015). No outbreak of vancomycin and linezolid resistance in staphylococcal pneumonia over a 10-year period. *PLoS ONE* **10(9), e0138895.**

Yiğit, N., Aktaş, A. E., Doğruman Al, F. and Ayyıldız, A. (2008). Identification of coagulase negative staphylococci isolated from blood cultures and determination of their methicillin resistance. *Turk Hijyen ve Deneysel Biyoloji Dergisi* **65(2), 61-66.**

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