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Antibiotic susceptibility of *Staphylococcus aureus* strains isolated from various clinical specimens in a tertiary hospital

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ABSTRACT

Aims: Multi-drug resistance is currently approaching alarming levels in *Staphylococcus aureus* (*S. aureus*) strains, which are often identified in community-acquired and hospital-acquired infectious illnesses. This study aimed to examine the antibiotic susceptibility of *S. aureus* strains isolated from patients treated in a tertiary state hospital for four years.

Methods: A retrospective analysis was performed on *S. aureus* strains (n=584) identified from clinical samples delivered to the Medical Microbiology Laboratory of Niğde Ömer Halisdemir University Training and Research Hospital for bacterial culture between January 2016 and December 2019. The strains were identified using both conventional methods and the VITEK 2 (bioMerieux) automated identification system. Antibiogram results were performed with the same automated system, taking into account EUCAST (the European Committee on Antimicrobial Susceptibility Testing) criteria.

Results: Strains were most commonly isolated from wound swabs (n=168, 28.7%) and blood cultures (n=108, 18.4%). Cefoxitin resistance ranged from 27.11% to 22.98% depending on the year. Among isolated *S. aureus* strains, the most antimicrobial resistance evolved against erythromycin (n=232). Vancomycin and teicoplanin resistance were not observed.

Conclusion: Multi-drug resistance and MRSA resistance still exist today. Due to the resistance rates, it was thought that more care should be taken in the use of erythromycin in the treatment. It is encouraging to observe that resistance to vancomycin and teicoplanin is absent in our hospital and also that resistance to trimethoprim-sulfamethoxazole is minimal in comparison to resistance to other antibiotics. This information about the susceptibility of *S. aureus* may be helpful in determining how to administer antibiotics.

Keywords: *Staphylococcus aureus*, antibiogram, multi-drug resistance

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INTRODUCTION

Staphylococcus aureus (*S. aureus*) is one of the most common opportunistic human pathogens. It is known for being able to get past the immune system and cause a wide range of infections.[1] *S. aureus* can cause bacterial infections in people that affect their bones, blood, skin, respiratory system and other soft tissues.[2] Moreover, *S. aureus* is also concerning as a pathogenicbacteria responsible for high morbidity and mortality worldwide.[3]

In 1880, Scotland-based physician Alexander Ogston made the historic discovery of *S. aureus* in patients with open wounds. *S. aureus* is a member of the *Staphylococcus* genus, *Firmicutes*; is positive for Gram stain, is 0.8 µm in diameter; appears under a microscope as a "string of grapes" and grows best at 37°C and pH 7.4.[4] The colonies on the blood agar plate are round, shiny and thick, with a diameter of 1-2 mm. *S. aureus* also has a capsule, the ability to create golden yellow pigment and the ability to break down mannitol. However, it does not produce spores or flagella. In addition, plasma coagulase, lactose fermentation and deoxyribonuclease tests are positive for *S. aureus*.[4,5] *S. aureus* is an osmotic stress and desiccation-tolerant bacteria that may survive in potentially dry and harsh environments.[6]

Because of its remarkable adaptability, *S. aureus* can become resistant to the majority of current antibiotics. Over the past few decades, *S. aureus* drug resistance has gradually increased as the pathogen has changed and medicines have been overused.[7] There are several different types of resistance mechanisms, such as enzymatic antibiotic inactivation (penicillinase and aminoglycoside-modification enzymes), alteration of the target with decreased antibiotic affinity (penicillin-binding protein 2a of methicillin-resistant

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S. aureus and D-Ala-D-Lac of peptidoglycan intermediates of vancomycin-resistant strains), trapping of the antibiotic (for vancomycin and possibly daptomycin) and efflux pumps (tetracycline and fluoroquinolones).[8] As a result, it is possible to identify multi-drug resistance as well as resistance to several drug classes. *S. aureus* infections are particularly problematic due to the frequently occurring antibiotic resistance in methicillin-resistant *S. aureus* (MRSA).[9] While hygiene and surveillance measures have reduced hospital-acquired MRSA infections in many countries, including the United States (US) and Europe, there has been an increase in less developed countries.[10]

Other than methicillin, beta-lactamase-sensitive beta-lactam antibiotics like penicillin and its derivatives are often found to be resistant. Vancomycin resistance, which is used as a last resort in the treatment of MRSA, is increasing day by day. Except for these antibiotics, they can adapt to and develop resistance to any antibiotic used in combination.[11] This situation complicates the treatment of infections caused by this microorganism. The presence of resistance, especially MRSA, causes significant problems in the success of treatment and even this situation reaches dimensions that may limit treatment options. In addition, it increases the cost of treatment. Continuous monitoring of antibiotic resistance surveillance is crucial in directing empirical treatment and establishing an appropriate antibiotic usage policy.[12] From this perspective, our research is aimed at investigating the antibiotic susceptibility of *S. aureus* strains isolated from patients treated in a tertiary state hospital between January 2016 and December 2019, to show the resistance profile of our hospital and to contribute about the choice of empirical treatment.

METHODS

The study was carried out with the permission of Niğde Ömer Halisdemir University Training and Research Hospital Ethics Committee (Date: 09.12.2021, Decision No: 2021/109). All procedures were performed adhering to the ethical rules and the Helsinki Declaration of Principles.

A retrospective analysis was done to determine the antibiotic susceptibility of *S. aureus* strains isolated from clinical samples (blood, sterile body fluids, sputum, urine, wound swab, abscess, tracheal aspirate, etc.) supplied to the medical microbiology laboratory of Niğde Ömer Halisdemir University Training and Research Hospital between January 2016 to December 2019. *S. aureus* isolates (n=584) were collected from culture samples received from different departments of the hospital. The inclusion criteria for study data were one sample from one patient and a second sample from another site of the same patient was not considered for the study.

The clinical samples that came to our laboratory from outpatients and/or inpatients in our hospital on the specified dates were incubated in an incubator at 35±2 °C for 18-24 hours after being inoculated on 5% Sheep Blood, Eosin Methylene Blue (EMB) and Chocolate agar media. In addition, blood samples taken from the patients were evaluated in the BacT/Alert 3D (bioMérieux, France) automated blood culture system. The blood culture that gave a positive signal was cultivated in the above media and incubated in an incubator for 18-24 hours at 35±2°C. Standard microbiological techniques such as Gram staining, colony morphology, the catalase test and the coagulase test were used to identify the pure isolated bacterial colonies.[13] The VITEK 2 (BioMerieux, France) automated identification system was used for the identification of the species and antibiotic susceptibility of Gram positive cocci with a positive coagulase test according to the manufacturer's instructions.[14] The interpretation of the minimum inhibitory concentration (MIC) results was based on the European Committee on Antimicrobial Susceptibility Testing (EUCAST) antimicrobial susceptibility guidelines.[15] The following antibiotics were tested: penicillin (P), oxacillin (OX), erythromycin (E), ciprofloxacin (CIP), tetracycline (TE), clindamycin (DA), cefoxitin (FOX), trimethoprim/sulfamethoxazole (SMT), rifampin (RA), gentamicin (CN), vancomycin (VAN), levofloxacin (LEV), linezolid (LNZ), tigecycline (TGC), amikacin (AK), ceftriaxone (CRO), ampicillin (AM), methicillin (ME) and ceftazidime (CAZ). The MIC value of cefoxitin (>4 mg/L) was used to determine methicillin resistance in stains.

Statistical Analysis

All statistical analyses were done using SPSS v.20.0 software (SPSS Inc., USA). The antimicrobial susceptibilities were compared using the Chi-square and Pearson Chi-square tests. A p value < 0.05 was considered statistically significant.

RESULTS

The number of *S. aureus* strains obtained from various patients was determined as 584. Antibiograms were performed with various antibiotics for each of these isolates. The study included 102 pediatric patients aged 0-17 years and 482 adult patients aged 18-95 years. The study included 254 female patients (44%) and 330 male patients (56%).

Out of 584 *S. aureus* isolated from various clinical specimens, the highest number of isolates were from wound swabs (n=168, 28.76%) and blood (n=108, 18.49%) (**Table 1**). *S. aureus* was detected in the highest number of samples from the intensive care unit (ICUs) (n=117).

Table 1: Distribution of various samples from different wards

Culture names	Departments								
	Intensive care units	Orthopedics and traumatology	Ear nose throat diseases	Family medicine	Child health and diseases	Urology	Infectious diseases and clinical microbiology	Others	Total
Joint fluid	-*	14	-	-	2	-	-	1	17
Wound	7	60	9	-	20	2	16	54	168
Tracheal aspirate	49	-	-	-	1	-	-	7	57
Blood	44	3	-	-	21	2	13	25	108
Urine	4	-	-	-	15	30	2	18	69
Throat	-	-	2	-	4	-	3	2	11
Ear	-	-	23	-	-	-	-	-	23
Sputum	2	-	-	-	1	-	-	9	12
Other	11	5	-	54	7	10	12	20	119
Total	117	82	34	54	71	44	46	136	584

*-: No sample

When all isolates were examined in our study, it was found that 20% were resistant to one or more antibiotics and 80% were susceptible. Among the isolates, erythromycin resistance (n=232) was the most common antibiotic.In our study, the results were evaluated according to years. When examined by years, the highest erythromycin resistance (40.42%) was

found in 2016 (**Table 2**). Similar to this, it was discovered that gentamicin and levofloxacin resistance dropped from 24.16% to 6.66% (p=0.05) and 29.31% to 12.66 (p=0.01), respectively. There was no vancomycin and teicoplanin resistance established from 584 strains. Cefoxitin, which is an indicator of MRSA resistance, was determined to be in the range of 27.11% to 22.98% among isolates. The highest cefoxitin resistance was detected in 2019 (27.27%). Generally speaking, a declining percentage of resistance is observed over time when the entire rates of resistance to all antibiotics are taken into account.

DISCUSSION

The spread of multi-drug-resistant organisms in hospitals is a public health problem that continues to challenge infection control and hospital epidemiology practices around the world. Numerous countries have created and implemented national healthcare-associated infection control and prevention policies.[15] Because of its high virulence and the dearth of effective medications for resistant strains, multi-drug resistance *S. aureus*, especially MRSA, is listed as one of the most significant antimicrobial resistant bacteria in the World Health Organization (WHO) Global Surveillance Report.[17] Therefore, the development of antibiotic resistance of *S. aureus* should be monitored by continuous research.

Treatment for penicillin-resistant *S. aureus* strains that emerged as a result of the widespread use of penicillin has begun with the use of methicillin. Later, in 1961, England became the first country to isolate methicillin-resistant strains.[18] Methicillin resistance is described as resistance to beta-lactam antibiotics that are not degraded by beta-lactamase. Several antibiotics, including erythromycin, clindamycin, tetracycline and aminoglycosides, can be resistant in MRSA.[19] The available antibiotic alternatives are limited as a result of multidrug resistance in MRSA. Combination antibiotic therapy should be used because one antibiotic is insufficient on its own.[18] Retrospective analysis of antimicrobial resistance in *S. aureus* isolates revealed that only 20% of them were resistant to one or more antibiotics in our research.

Increasing methicillin resistance in both community-acquired and hospital-acquired staphylococci is also an important problem.[20] MRSA infection rates change between continents, nations, hospitals and even between wards in the same hospital.[21] The prevalence of MRSA varies over the world, ranging from 16% to 55% in Africa and the Middle East 12.4% to 30%, in the USA 29% to 43% andSoutheastAsianlocations 20%to 30%and MRSA prevalence reaches 40% in Greece where antimicrobial therapy resistance is still widespread.[21,22]

The antibiotic cefoxitin is more efficient than the oxacillin, which was used to show MRSA resistance.[23,24] As a result, the decline in MRSA resistance coincides with the decline in cefoxitin resistance. According to our study, cefoxitin resistance ranged from 27.11% to 22.98% depending on the years. In a retrospective study conducted by Ayvalık et al.[25] in Turkey, MRSA was determined as 20.7% in intensive care patients. Similarly, in a retrospective study conducted in a city hospital in Turkey between 2017 and 2019, methicillin resistance was reported as ranging from 31.2% to 31.9%.[26] The percentages of MRSA were recorded as 23.6%, in the 2016 annual reports of the National Antimicrobial Resistance Surveillance System (UAMDSS), which the Public Health Institution of Turkey initiated with the involvement of the laboratory. According to the European Antimicrobial Resistance Surveillance System 2016 (EARSS-Net 2016) Report, the European MRSA average is determined at 13.7%.[27] Although the statistics from our study overlap with the average for Turkey, they nevertheless demonstrate that our MRSA rate is higher than that of the European data.

Drug-resistant strains of MRSA are becoming more prevalent, which is related to multidrug resistance. Antibiotics that are frequently used to treat MRSA include macrolides, clindamycin, quinolones, glycopeptides, tetracycline and trimethoprim/sulfamethoxazole.[28] However, following accordance with the limiting antibiogram guidelines advised by EUCAST, the first treatment options are benzyl penicillin, erythromycin, clindamycin and trimethoprim/sulfamethoxazole in group A. The group B antibiotics ciprofloxacin, teicoplanin and vancomycin are preferred for the treatment of infections caused by *S. aureus* strains resistant to these antibiotics. In the absence of any sensitive antibiotics in the first two groups, group C antibiotics such as linezolid, tigecycline and daptomycin should be selected.[29] Resistance to erythromycin and clindamycin has been increasing recently. Results of our study demonstrate that erythromycin resistance at our hospital ranged from 40.42% to 30.13% and clindamycin resistance ranged from 26.47% to 14.89%. Despite the fact that erythromycin resistance decreased during the research period, erythromycin resistance was higher than methicillin resistance in our study. Similarly, erythromycin resistance was found to be 30.4% and clindamycin resistance was found to be 20%, both higher than MRSA rates in the study by Çay et al.[30] Erythromycin resistance was reported to be 45.1% in MRSAs in a study conducted at a university hospital in Turkey between 2018 and 2019.[31] In a similar study carried out in our country

Table 2. Antibiotic resistance profiles of *Staphylococcus aureus* strains between January 2016- December 2019

Antibiotics	2016			2017			2018			2019			Total (n)	P**
	R (n)	S (n)	R-Rate*	R (n)	S (n)	R-Rate	R (n)	S (n)	R-Rate	R (n)	S (n)	R-Rate		
Erythromycin	57	84	40,42	74	121	37,94	78	127	38,04	23	52	30,13	616	0,564
Gentamicin	29	91	24.16	24	133	15.28	10	113	8.13	1	14	6.66	415	0,05
Clindamycin	36	100	26.47	42	150	21.87	52	168	23.63	15	82	14.89	645	0,241
Levofloxacin	34	82	29.31	26	142	15.47	19	131	12.66	0	0	0	434	0,01
Cefoxitin	45	121	27.11	50	155	24.39	37	124	22.98	10	26	27.27	568	0,818
Trimethoprim/sulfamethoxazole	20	108	15.62	15	163	8.42	23	199	10.36	8	87	7.60	623	0,188
Vancomycin	0	50	None	0	69	None	0	66	None	0	7	None	192	-
Teicoplanin	0	46	None	0	52	None	0	43	None	0	2	None	143	-
Others***	2	13	3.17	13	48	21.31	37	173	17.61	44	187	19.05	517	0,896
Total Resistance Rates	223	695	24.29	244	1033	19.10	256	1144	18.28	101	457	18.10	4153	

R: Resistance, S: Susceptible, *R-Rate (%): Percentage of antibiotic resistance during the years, **p: Chi- Square p value, ***Others: penicillin (P), oxacillin (OX), ciprofloxacin (CIP), tetracycline (TE), rifampin (RA), linezolid (LNZ), tigecycline (TGC), amikacin (AK), ceftriaxone (CRO), ampicillin (AM), methicillin (ME) and ceftazidime (CAZ)

between 2016 and 2019, erythromycin resistance of MRSA strains was found to be 60%, while clindamycin resistance was revealed to be 39%.[32] We probably assume that, due to the rise in erythromycin resistance, it is commonly preferred in empirical treatment and widely utilized in patients with penicillin allergies.

The frequent use of glycopeptide antibiotics in MRSA infections has resulted in decreased susceptibility to vancomycin and teicoplanin.Because of its similar mechanism of action and minimal side effects, teicoplanin is commonly used as an alternative to vancomycin.[33] In contrast, no isolates resistant to teicoplanin and vancomycin are identified in this study. Vancomycin resistance has not been reported in MRSA strains in our country in the data of the UAMDSS (2016) and the Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR, 2019).[32] In a number of studies carried out in our country, resistance to vancomycin and teicoplanin was also not detected.[12,29,32] We assume that the lack of glycopeptide resistance is attributable to the fact that glycopeptides were not used as first-line therapy in *S. aureus* infections at our hospital. Even so, it should be considered that vancomycin-intermediate *S. aureus* (VISA) strains may occur during treatment with vancomycin.[32] Although we detected any strains that were vancomycin or glycopeptide resistant, it is crucial to routinely monitor glycopeptide resistance at our hospital.

In our study, trimethoprim-sulfamethoxazole resistance was discovered at rates ranging from 15.62% to 7.60%. When resistance rates are considered in our study, trimethoprim-sulfamethoxazole is found to be the most effective antibiotic after vancomycin and teicoplanin. Tanriverdi et al.[31] reported 14.6% trimethoprim/sulfamethoxazole resistance in MRSA isolates in a two-year retrospective study. Trimethoprim-sulfamethoxazole resistance declined from 16.4% to 10.7% in hospital-acquired MRSA isolates across a fifteen-year follow-up investigation of the resistance profile of *S. aureus* in our nation.[34] Trimethoprim sulfamethoxazole is regarded as an alternate antibiotic for the treatment of *S. aureus* infections without presenting a significant risk, in accordance with our data.

Levofloxacin resistance in the study was found to have reduced from 29.31% to 12.66%. Levofloxacin resistance ranged from 31.2% to 1.5% in prior investigations conducted in Turkey.[31,32] Similarly, gentamicin resistance decreased from 24.16% to 6.66% over a four-year period in this research. However, according to research conducted in Turkey, the percentage of gentamicin resistance ranges from 5 to 90%.[29] Hospitals should establish their own policies because of the broad range of gentamicin resistance seen in our country. Gentamicin and levofloxacin can still be utilized as an alternative antibiotic for treatment *S. aureus* infections at our hospital.

When the data collection units in our study were evaluated, it was found that intensive care patients had a higher percentage of *S. aureus* isolates than those in other units. In order to prevent the spread of MRSA in infections, it has been found that intensive care and invasive treatments are crucial. According to our research, a decreasing trend was observed in erythromycin and trimethoprim-sulfamethoxazole resistance rates. Nonetheless, it was determined that it should be applied to MRSA strains with greater caution in terms of resistance rates. No resistance was observed for vancomycin and teicoplanin. For this reason, it was thought that the use of vancomycin and teicoplanin would be appropriate in patients with multi-drug resistance who were treated in our hospital and had treatment difficulties. In addition, gentamicin and levofloxacin might be utilized as alternatives in MRSA infections in our hospital. Considering the resistant *S. aureus* strains isolated from our hospital, this is an encouraging outcome. Nonetheless, we think that regular monitoring of hospital resistance profiles together with the required infection prevention measures is important.

CONCLUSION

Infection with multidrug-resistant bacteria leads to high morbidity and mortality. Antimicrobial resistance surveillance is critical for improving infection control, antibiotic prescriptions and prevention policies.[35] Reduced usage of broad-spectrum antibiotics for common infections should be the main goal. As a result of this research, it was determined that the resistance rate among the isolates was mostly against erythromycin. It is quite encouraging that the tested strains did not have resistance to vancomycin and teicoplanin. The present study, which provides information on the antibiotic susceptibility of *S. aureus*, may be helpful in determining how to prescribe antibiotics.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Niğde Ömer Halisdemir University Ethics Committee (Date: 09.12.2022, Decision No: 2021/109).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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