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Distribution of Clinical *Staphylococcus aureus* Isolates and Antibiotic Resistance Profile: Three-Year Data

Klinik Örneklerden İzole Edilen *Staphylococcus aureus* İzolatlarının Sıklığı ve Antibiyotik Duyarlılık Sonuçlarının Değerlendirilmesi: Üç Yıllık Veri

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Abstract

Aim: Staphylococci cause community-acquired and hospital-acquired infections, and *Staphylococcus aureus* is one of the leading agents. In the last decades antibiotic resistance of *S. aureus* showed a growing trend especially regarding methicillin-resistant *S. aureus* (MRSA), vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA), since MRSA is in the "Serious Threat List" of CDC. The aim of this study was to investigate the prevalence of *S. aureus* species and to evaluate susceptibilities to antimicrobial agents in a state (tertiary) hospital.

Material and Method:: Clinical cultures from various samples (urinary tract, respiratory, wound, abscess, tissue, catheter and external auditory) obtained from January 2017 to December 2019 in Balıkesir Atatürk City Hospital were included in the study. Isolated *S. aureus* strains and their antibiotic susceptibilities were retrospectively evaluated and annual results were statistically compared. Blood, sterile body fluid cultures and surveillance data were excluded.

Results: A total of 765 *S. aureus* strains were isolated. 165 *S. aureus* strains were found as methicillin resistant (MRSA; 21.9%). There was not any statistically significant difference in MRSA rates among evaluated years (p=0.772). There was not any strain that was resistant to vancomycin, teicoplanin and/or linezolid. The highest rate was observed in penicillin resistance (n=646/728, 88.7%). There was not any statistically significant alteration in the resistance rates of all tested antibiotics during the three-year period.

Conclusions: Despite CAESAR report indicating Turkey to have a struggle for AMR in *S. aureus*, this data showed a "steady-state" mode, while UAMDSS stated dwindling MRSA rates. Local and/or national antimicrobial stewardship programs are in effect in Turkey, but further measures are required.

Keywords: *S. aureus*, methicillin, MRSA, EUCAST, CLSI

Öz

Amaç: Stafilokoklar hem toplum hem de hastane kaynaklı enfeksiyonlara neden olabilmektedir ve *Staphylococcus aureus* bu cinste en başta gelmektedir. Son yıllarda, başta metisilin dirençli *S. aureus* (MRSA), vankomisine orta düzeyde duyarlı *S. aureus* (VISA) ve vankomisine dirençli *S. aureus* (VRSA) olmak üzere *S. aureus* bakterisinin antibiyotik direnci sorunu öyle ciddileşmiştir ki CDC, MRSA'yı "Ciddi Tehdit" kategorisine almıştır. Bu çalışmadaki amaç, üçüncü basamak bir hastanede çeşitli klinik örneklerden izole edilen *S. aureus* suşlarının sıklığını ve antibiyotik duyarlılıklarını araştırmaktır.

Gereç ve Yöntem: Çeşitli klinik örneklerin (üriner sistem, solunum, yara, apse, doku, katater ucu ve dış kulak yolu) Ocak 2017'den Aralık 2019'a kadar Balıkesir Atatürk Şehir Hastanesi'ndeki kültürleri çalışmaya dahil edilmiştir. Üremiş *S. aureus* suşları ve antibiyotik duyarlılıkları geriye dönük incelenmiş ve yıllara göre istatistiksel olarak karşılaştırılmıştır. Kan kültürü, steril vücut sıvıları ve sürveyans tarama verileri dahil edilmemiştir.

Bulgular: Toplamda 765 *S. aureus* suşu izole edilmiştir ve bunların 165 tanesi metisilin dirençlidir (MRSA; %21.9). Yıllara göre MRSA oranları arasında istatistiksel fark bulunamamıştır (p=0.772). Vankomisin, teikoplanin ya da linezolide dirençli bir suşa rastlanmamıştır. En yüksek direnç oranı penisiline karşı bulunmuştur (n=646/728, %88.7). Üç yıllık dönemde antibiyotik direncinde hiçbir antibiyotik için anlamlı fark gözlenmemiştir.

Sonuç: Türkiye'nin *S. aureus* için antibiyotik direnci sorunu olduğunu işaret eden CAESAR verilerine rağmen, bu çalışmadaki veriler durağan seyir göstermekte ve UAMDSS de ise, MRSA için azalan bir eğilim görülmektedir. Yerel ve/veya ulusal antimikrobiyal yönetimi programları Türkiye'de de aktiftir, ancak daha sert ve geniş önlemlere ihtiyaç vardır.

Anahtar Kelimeler: *S. aureus*, metisilin, MRSA, EUCAST, CLSI

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INTRODUCTION

Staphylococci cause community-acquired and hospital-acquired infections, that can be mild to severe. *Staphylococcus aureus*, with a very wide infectious spectrum, is one of the leading causing agents. Bloodstream infections (BSIs), infective endocarditis (IE), skin and soft tissue infections, urinary tract infections (UTIs), osteoarticular and pulmonary infections are the most frequent clinical manifestations. In the last two decades, there is an increasing trend in healthcare-associated infections such as IE and prosthetic infections, and community-acquired skin and soft tissue infections.[1]

The growing problem of antimicrobial resistance (AMR) (particularly β-lactam antibiotics) and dwindling choices of treatment options have made *S. aureus* as one of the greatest concerns of not only microbiology societies but also public health, that evolves to a health crisis. The worldwide spread of methicillin-resistant *S. aureus* (MRSA) has created uptight laboratories due to its "front runner" position as both community-acquired and hospital-acquired infections.[2,3] Surveillance data from Europe indicates a massive spread of MRSA from the Mediterranean zone to Nordic countries (Denmark, Norway, Sweden), so such that even 35-50% resistance rates are observed in Turkey, Italy, Greece and Portugal, but it is slightly lower than 5% in the Nordic area.[2] In addition, vancomycin, which is a preferable glycopeptide antibiotic against MRSA, has begun to lose its efficiency, since vancomycin-intermediate *S. aureus* (VISA) and eventually vancomycin-resistant *S. aureus* (VRSA) strains were observed.[2-4]

Local, national and international monitoring of antibiotic resistance data take a crucial role to design and activate strong measures. Antimicrobial stewardship policies and study groups endorse all laboratories and infection control committees (local and national) to carry out their own surveillance studies in order to guide their healthcare facilities. Such surveillance studies indicate that *S. aureus* will remain to be a major part of microbiological science and routine laboratory studies, since its clinical isolation and AMR rates are still high.[4] The aim of this study was to investigate the prevalence of *S. aureus* species and to evaluate susceptibilities to antimicrobial agents, including their recent statistical trend in the last 3 years in a state (tertiary) hospital.

MATERIAL AND METHOD

Ethical Approval: Approved by The Ethical Board of Balıkesir University, Faculty of Medicine (Date:11 Nov 2020 / Decision Number: 2020/203).

S. aureus isolates obtained from various clinical samples including urinary tract, respiratory, wound, abscess tissue, catheter and external auditory that were sent for bacterial cultures from January 2017 to December 2019 in Balıkesir Atatürk City Hospital (tertiary center) were included in the study. Isolated *S. aureus* strains and their antibiotic susceptibilities were retrospectively evaluated. A total of 765 *S. aureus* isolates that were accepted as infectious agents were included in the study. Blood and sterile body fluid cultures (SBFs) were excluded because of previously being subject of other studies. Surveillance data were also excluded.

The only first sample was included for repetitious samples from the same patient. Cultures were applied and incubated with conventional methods (Urine cultures: 35-37°C, 48 h, ambient atmosphere with 5% sheep blood agar, eosine methylene blue agar; other samples: 35-37°C, 48 h, 5% CO_2 atmosphere with 5% sheep blood agar, eosine methylene blue agar, chocolate agar) (RTA Laboratories, Kocaeli, Turkey). Grown colonies were identified by gram staining, hemolysis feature, colorimetric change in Chapman agar, catalase test, slide and tube coagulase tests and Phoenix™ 100 automated system (Becton Dickinson, MA, USA).

Antimicrobial susceptibility testing was performed by Phoenix™ 100 automated system (Becton Dickinson, MA, USA) according to the instruction of the manufacturer and the results were interpreted according to the guidelines of The European Committee on Antimicrobial Susceptibility Testing (EUCAST, valid from 01.01.2019, v.9). In particular, minimum inhibitory concentrations (MICs) of cefoxitin, tetracyclines and glycopeptides were used for screening due to "screen only" interpretations of EUCAST. *S. aureus* ATCC 29213 was used as quality control strain.[5]

Statistical Analysis: SPSS 22.0 (SPSS INC, Chicago, IL, USA) programme was used. Annual antimicrobial resistance ratios of 2017, 2018 and 2019 were compared by Chi-squared distribution test. p levels<0.05 were accepted as statistically significant.

RESULTS

A total of 765 *S. aureus* isolates were detected from various samples (n=239, 31.2% in 2017; n=283, 36.9% in 2018 and n=243, 31.9% in 2019). While 53.1% of samples were wound/tissue, 17.9% were endotracheal aspirate, 13.3% were urinary tract samples, 7.1% were sputum, 5.6% were external auditory samples, 3.0% were catheter. 42.4% of strains were isolated from outpatients, 33.7% were from clinics/inpatients, 23.9% were from intensive care units (ICUs).

A total of 165 *S. aureus* strains were found as methicillin-resistant (21.9%) (majority of them were from inpatients – 85.1%). There was not any statistically significant difference in MRSA rates among evaluated years (p=0.772) (n=52, 22.8% in 2017; n=56, 19.8% in 2018; n=57, 23.5% in 2019). The highest rate was observed in penicillin resistance (n=646/728, 88.7%). Promisingly, there was not any strain that was resistant to vancomycin, teicoplanin and/or linezolid. Distribution of *S. aureus* resistance data among years was presented in **Table 1** and its overlook with The Turkish National Antimicrobial Resistance Surveillance System (UAMDSS) and Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR) were presented in **Table 2**, respectively.

Table 1. Antibiotic resistance profiles of *Staphylococcus aureus* species

Years	2017			2018			2019			Overall			P value
Antibiotics	**S (n)**	**R (n)**	**R-Rate (%)**	**S (n)**	**R (n)**	**R-Rate (%)**	**S (n)**	**R (n)**	**R-Rate (%)**	**S (n)**	**R (n)**	**R-Rate (%)**	
Benzylpenicillin[1]	13	190	93.6	34	246	87.9	35	210	85.7	82	646	88.7	0.186
Daptomycin	220	0	None	278	0	None	236	0	None	734	0	None	NA
Vancomycin	239	0	None	283	0	None	243	0	None	765	0	None	NA
Teicoplanin	227	0	None	279	0	None	241	0	None	747	0	None	NA
Linezolid	231	0	None	281	0	None	243	0	None	755	0	None	NA
Clindamycin[6]	178	43	19.5	244	37	13.2	212	32	13.1	634	112	15.0	0.390
Tetracycline[7]	161	46	22.2	229	49	17.6	203	38	15.8	593	133	18.3	0.414
Co-Trimoxazole	200	1	0.5	252	0	None	223	11	4.7	675	12	1.7	0.071
Fusidic acid	177	32	15.3	254	26	9.3	208	35	14.4	639	93	12.7	0.393
Cefoxitin[1,2,3]	177	52	22.7	227	56	19.8	184	57	23.7	588	165	21.9	0.772
Levofloxacin	168	31	15.6	251	27	9.7	208	34	14.0	627	92	12.8	0.393
Ciprofloxacin	189	39	17.1	248	31	11.1	207	36	14.8	644	106	14.1	0.474
Gentamicin[4]	184	48	20.7	233	48	17.1	199	44	18.1	616	140	18.5	0.856
Erythromycin[5]	173	60	25.8	232	49	17.4	198	47	19.2	603	156	20.6	0.343

NA: Not Applicable; S: Susceptible; R: Resistant; R-Rate: Resistance Rate

1. Isolates that were susceptible to both benzylpenicillin and cefoxitin were reported as susceptible to all penicillins. Isolates that were resistant to benzylpenicillin but susceptible to cefoxitin were reported as susceptible to β-lactam + β-lactamase inhibitors, isoxazolylpenicillins and nafcillin. Isolates that were resistant to cefoxitin were reported resistant to all penicillins.
2. Isolates that were susceptible to cefoxitin were reported as susceptible to cephalosporins except cefixime, ceftazidime, ceftazidime-avibactam, ceftibuten and ceftolozane-tazobactam.
3. Cefoxitin MIC>4 mg/L was accepted as resistant.
4. Gentamicin was reported with a warning that indicates aminoglycosides must be used in combination therapies for systemic treatments.
5. Erythromycin was reported with a warning that indicates it also reflects azithromycin and clarithromycin susceptibility.
6. Inducible clindamycin resistance was not tested.
7. Tetracycline was reported with a warning that indicates it may also reflect doxycycline and minocycline susceptibility. In case of resistance and necessity, clinicans were endorsed to consult laboratory.

Table 2: Data comparison with UAMDSS ve CAESAR reports

Years	Present Studyd	UAMDSS						CAESAR
		2011[c]	2012[c]	2013[c]	2014[c,d]	2015[c,d]	2016[c,d]	2020[c,d]
Antibiotics		R-Rate (%)						
MRSA	21.9	31.5	25.1	26.9	27.0	25.0	23.6	31.0
Ciprofloxacin[a]	14.1	ID	ID	ID	15.0	14.0	14.5	13.0
Levofloxacin[a]	12.8							
Teicoplanin[b]	None	ID	ID	None	ID	ID	None	ID
Vancomycin[b]	None	None	None	None	None	None	None	None
Linezolid	None	1.0	None	None	None	1.0	None	None

UAMDSS: Turkish National Antimicrobial Resistance Surveillance System; MRSA: Methicillin-Resistant *Staphylococcus aureus*; CAESAR: Central Asian and European Surveillance of Antimicrobial Resistance report; ID: Insufficient data; [a]UAMDSS and CAESAR reported fluoroquinolones as one data; [b]Confirmed with MIC; [c]CLSI results; [d]EUCAST results

DISCUSSION

Staphylococcus aureus is a commensal but also a common cause of human infections with a wide spectrum infectious profile, including especially the skin and other soft tissue, bone, bloodstream, and respiratory infections. The pathogen is very famous with a remarkable success in developing resistance to each new class of antistaphylococcal antimicrobial drugs, including the penicillins, tetracyclines, glycopeptides, and others, which emergingly limits antimicrobial therapies. Since first identification of methicillin resistance in the 1960s, it has become a growing issue and consequently, Centers for Disease Prevention and Control (CDC) pronounced MRSA as a "serious threat" and World Health Organization (WHO) listed MRSA along with vancomycin-intermediate and resistant *S. aureus* (VISA and VRSA) high priority pathogens that urgently require new antibiotics to fight against.[6-8]

There are several reports about the epidemiology of MRSA infections. Pediatric and geriatric population, athletes, military staff, persons in institutionalized populations (such as prisons), individuals with an indigenous background or in urban and users of injectable drugs, patients with HIV positivity and cystic fibrosis, and persons with strong healthcare facility contact stated as high risk population. Besides nasal one, colonization (sometimes persistant) and intensive antibiotic usage creates a major risk in particularly ICUs. Continuous and regular screening claimed to have crucial effect in overcoming the issue.[9] International organizations such as WHO, CDC and European Center for Disease Prevention and Control (ECDC), and national authorities endorse laboratories to perform a continuous surveillance, since all reports indicate that overcoming AMR is a multidisciplinary approach and requires strict policies from top level (international and national

authorities) to end-point healthcare centers. Surveillance in antimicrobial resistance and antibiotic consumption, limited reporting of susceptibility results, prohibiting prescribing and usage of particular antibiotics except compelled clinical necessity can only be achieved by local, regional and national AMR data. In European countries, annual CAESAR reports indicate a serious problem, especially for Turkey. Despite of CAESAR only considers BSIs and cerebrospinal fluid (CSF) isolates, results showed Turkey had a high rate of MRSA (>30%).[10] Accordingly, UAMDSS results of MRSA were also over than 23%, however, promisingly, there was a steady dwindling trend.[11] In a ten-year BSI report from Turkey, MRSA rate was 32%, however MR in coagulase-negative staphylococci was over than 90%.[12] Even higher MRSA rates were reported in other studies (28-53%).[13] It is also fortunate that neither UAMDSS nor CAESAR reports showed glycopeptide and linezolid resistance, which was totally compatible with the findings of this study. However, as seen in previous reports, there are clues of a future perspective (linezolid resistance: 0-13.3%; vancomycin resistance: 0-2.4%).[13] Locally, in another tertiary hospital focusing on BSIs, Kula-Atik et al. reported 28% of MRSA among *S. aureus* isolates, along with absence of any glycopeptide or linezolid resistance. In their summary of results from Turkey, MRSA rates vary in a wide range (12-62%), which is hard to speculate, that might be probably because of sampling differences.[14] Previously, from our center, 41% of *S. aureus* isolates from blood cultures were found to be MRSA and only one MRSA isolate was detected from SBFs in three- and four-year periods.[15,16] In addition, fluoroquinolone resistance did not seem to change over years in UAMDSS, which was also compatible with CAESAR data and findings of this study. In this study, there was not any statistically significant alteration in the resistance rates of all tested antibiotics during the three-year period.

There were some limitations of this study. First, this study was based on EUCAST methodology, but several studies including UAMDSS were mainly based on The Clinical and Laboratory Standards Institute (CLSI) techniques. Even though lower susceptibility rates were reported with EUCAST, our resistance rates did not show any such pattern.[17] Comparison of EUCAST and CLSI is beyond the scope of this study. Both techniques are mainly reference methods and indicate therapeutic success. Thus, we believe our data shows a good perspective for the condition of our local area and national status. Secondly, blood and SBF cultures were excluded, since they were published in previous studies by other authors. In addition, we did not use disk diffusion method, especially to observe oxacillin and inducible clindamycin resistance. Thirdly, we could not reach to the data before 2017 because of hospital software changes. Furthermore, it was unable to discriminate resistance ratios according to types of clinics, especially ICUs. Finally, we could not reach to antibiotic consumption data of our area in order to compare with resistance ratios, however, defined daily doses (DDD) of antibiotic consumptions were previously reported as seriously high in Turkey.[18,19]

CONCLUSION

Antibiotic consumption is strongly associated with AMR. In the Organization for Economic Co-operation and Development (OECD) 2015 report, Turkey had a really bad ration card and Turkey's all efforts created only a limited success (20). Despite dwindling MRSA rates in UAMDSS, CAESAR report indicates that Turkey seems to be in the beginning phase of this struggle (10,11). Local and/or national antimicrobial stewardship programs are in effect in Turkey, but further measures are required.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approved by Ethical Board of Balıkesir University, Faculty of Medicine. Date: 11.11.2020 Number: 2020/203.

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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