Araştırma Makalesi/Original Article
Makale Dili "İngilizce"/Article Language "English"

Türk Hijyen ve Deneysel Biyoloji Dergisi

Evaluation of frequency, antimicrobial resistance and multidrug resistance patterns of methicillin-resistant *Staphylococcus aureus* isolates at a university hospital in Northern Cyprus, 2016 to 2020

Kuzey Kıbrıs'ta bir üniversite hastanesinde metisilin-dirençli *Staphylococcus aureus* izolatlarının görülme sıklığı, antimikrobiyal direnç ve çoklu ilaç direnci paternlerinin değerlendirilmesi, 2016-2020

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ABSTRACT

Objective: *Staphylococcus aureus* is a major human pathogen which is responsible for a wide variety of clinical manifestations both in nosocomial and community settings. The presence of methicillin-resistant *Staphylococcus aureus* (MRSA) limits treatment options. There are major gaps in literature regarding the epidemiological and antimicrobial resistance characteristics of *S. aureus* in Northern Cyprus. This study aims to define the frequency of MRSA in a major hospital in Northern Cyprus and determine MRSA susceptibility to currently available antimicrobials in order to define the most effective regimen for the treatment of *S. aureus* infections.

Methods: Four hundred and forty-nine clinical samples collected between January 2016 to December 2020 were retrospectively included in the study. Samples were cultured on Eosin-Methylene Blue (EMB) and 5% sheep blood agar and were incubated at 35°C for 24-48 h. Laboratory identification of isolates and antimicrobial

ÖZET

Amaç: *Staphylococcus aureus*, hem hastane hem de toplum kaynaklı enfeksiyonlara neden olabilen önemli bir patojendir. Metisilin-dirençli *S. aureus* (MRSA) izolatlarının varlığı tedavi seçeneklerini sınırlamaktadır. Kuzey Kıbrıs'ta *S. aureus*'un epidemiyolojik ve antimikrobiyal direnç özelliklerine ilişkin literatürde kısıtlı veri bulunmaktadır. Bu çalışmada, hastanemizde MRSA görülme sıklığının belirlenmesi ve hastalardan izole edilen MRSA izolatlarında antibiyotik direnç oranlarının tespit edilerek en etkili tedavi seçeneklerinin tanımlanması amaçlanmıştır.

Yöntem: Ocak 2016-Aralık 2020 tarihleri arasında izole edilen 449 izolat retrospektif olarak çalışmaya dahil edilmiştir. Örneklerin Eozin Metilen Mavisi (EMB) ve %5 koyun kanlı agarlara ekimleri yapılmış ve 24-48 saat süresince 35°C'de inkübatörde inkübasyona bırakılmıştır. İzolatların tanımlanması ve antibiyotik duyarlılık testleri için Vitek-2 (bioMérieux, Fransa) otomatize sistem kullanılmıştır. Antibiyotik duyarlılığı,

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Geliş Tarihi / Received : 24.05.2022
Kabul Tarihi / Accepted : 03.01.2023

DOI ID : 10.5505/TurkHijyen.2024.24892

Baddal B, Potindji TMF, Güler E. Evaluation of frequency, antimicrobial resistance and multidrug resistance patterns of methicillin-resistant *Staphylococcus aureus* isolates at a university hospital in Northern Cyprus, 2016 to 2020. Turk Hij Den Biyol Derg, 2024; 81(1): 11 - 22

susceptibility testing have been performed by Vitek-2 (bioMérieux, France) automated identification and susceptibility testing system. Antibiotic susceptibility was assessed according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria. Multi-drug resistance (MDR4) was determined by analyses of beta-lactam resistance plus nonsusceptibility to three additional classes of antimicrobial drugs. Data analysis was performed using SPSS Statistics Software version 23. A p value <0.05 was considered as statistically significant.

Results: Of the 449 *S. aureus* isolates, 40.5% (n=182) were MRSA. In the inpatients group, MRSA infection rate was statistically higher (p=0.001) compared to outpatients. A significant correlation was observed between older age and MRSA infection. MRSA isolates exhibited higher resistance to erythromycin (85.4%), clindamycin (52.9%), ciprofloxacin (23.8%), levofloxacin (19.8%), tetracycline (68.0%), fosfomycin (13.0%), rifampicin (12.0%) and tobramycin (11.1%) compared to MSSA isolates (p<0.05). MDR was detected in 30.8% of the isolates. All isolates, MRSA and MSSA, showed high susceptibility to daptomycin, linezolid, vancomycin, fusidic acid, teicoplanin and gentamicin. The rate of MDR MRSA was observed to decrease statistically in the post-pandemic period compared to pre-pandemic period (p=0.0001).

Conclusion: Over the five-year period, of the study, MRSA isolates have shown an increased resistance to several antibiotics. Therefore, the Infection Control Committee should work actively and inappropriate antibiotic use should be limited in order to prevent the spread of MDR pathogens.

Key Words: Methicillin-resistant *Staphylococcus aureus*, infection, hospital, frequency, resistance patterns, Northern Cyprus

Avrupa Antimikrobiyal Duyarlılık Test Komitesi - European Committee on Antimicrobial Susceptibility Testing (EUCAST) standardlarına göre değerlendirilmiştir. Çoklu ilaç direnci (ÇİD4), beta-laktam direnci artı üç antimikrobiyal ilaç sınıfına karşı duyarlılık analizleriyle belirlenmiştir.

Bulgular: 449 *S. aureus* izolatının %40,5'i (n=182) MRSA olarak tespit edilmiştir. İzole edilen MRSA sayısı yatan hastalarda istatistiksel olarak anlamlı derecede daha yüksek bulunmuştur (p=0,001). İleri yaş ile MRSA enfeksiyonu görülme sıklığı arasında pozitif yönde anlamlı bir ilişki gözlenmiştir (p<0,001). MRSA izolatları, MSSA izolatlarına kıyasla, eritromisin (%85,4), klindamisin (%52,9), siprofloksasin (%23,8), levofloksasin (%19,8), tetrasiklin (%68,0), fosfomisin (%13,0), rifampisin (%12,0) ve tobramisin (%11,1) antibiyotiklerine daha yüksek direnç göstermiştir (p<0,05). İzolatların %30,8'inde ÇİD tespit edilmiştir. Tüm MRSA ve MSSA izolatları, daptomisin, linezolid, vankomisin, fusidik asit, teikoplanin ve gentamisine karşı yüksek duyarlılık göstermiştir. Pandemi öncesi döneme göre (2016-2019), pandemi sonrası (2020) ÇİD MRSA suşlarında istatistiksel olarak anlamlı bir düşüş belirlenmiştir (p=0,0001).

Sonuç: Çalışmanın beş yıllık süresi boyunca, MRSA izolatları çeşitli antibiyotiğe karşı artan bir direnç göstermiştir. Bu sebeple, ÇİD patojenlerin yayılımının önlenmesi adına, Enfeksiyon Kontrol Komitesi'nin aktif olarak çalışması ve uygunsuz antibiyotik kullanımının kısıtlanması gerektiği düşünülmektedir.

Anahtar Kelimeler: Metisilin-dirençli *Staphylococcus aureus*, enfeksiyon, hastane, görülme sıklığı, direnç paternleri, Kuzey Kıbrıs

INTRODUCTION

The steady rise of antibiotic resistance (AR) is one of the major challenges of healthcare systems worldwide (1) and is currently considered as a global pandemic (2–4). World Health Organization (WHO) reports indicate that the current research and development (R&D) pipeline does not provide the necessary interventions and initiatives for adequate antimicrobial discovery (5). According to the 2017 WHO priority pathogens list, categorized according to the urgency of need for new antibiotics as critical, high and medium priority, methicillin-resistant *Staphylococcus aureus* (MRSA) remains a high priority pathogen (6). MRSA has been reported to become increasingly drug-resistant in both hospital and community settings, and continues to be a major cause of morbidity and mortality worldwide (7). As a versatile bacterium, MRSA causes skin and soft-tissue infections (SSTIs), endocarditis, respiratory, nosocomial and serious bloodstream infections often complicated by metastatic infections (8–10) .

Dramatic changes in the antimicrobial susceptibility profiles of *S. aureus* have been globally reported rendering treatment of *S. aureus* infections challenging for clinicians, and limiting options (11,12). However, several current alternatives are actively being introduced, hence expanding the range of drug choices against MRSA (13–15). MRSA expresses resistance to methicillin and most of the currently available ß-lactams via carriage of either *mecA*, or one of the several allotypes *mecB*, *mecC* or *mecD* (16,17). These genes may be located on SCC*mec* as well as plasmids, and encode the production of a low affinity penicillin binding protein (PBP): PBP2' (18,19). Apart from production of PBPs with modified affinities for ß-lactam drugs, MRSA may exhibit other drug inactivation pathways such as production of penicillinases which hydrolyze the beta-lactam ring of penicillin (20).

The frequency of MRSA varies among different countries or in hospitals and healthcare facilities within the same country. Resistance Surveillance Network (EARS-Net) 2018 report analysis of 30 European Union (EU) and European Economic Area (EEA) countries suggest that, despite previous diminished rates of MRSA, several EU/EEA countries are still reporting high level burden of MRSA infections (21). In Turkey, the proportion of MRSA were reported to be in 22.7% in 2016, 25.8% in 2017, 29.6% in 2018, 31.3% in 2019 and 33.4% in 2020 (22). Such increasing trends of antibiotic resistance signify an urgent necessity to address management and prevention strategies by implementing continuous surveillance, a key element to determine the burden of MRSA in healthcare facilities and high-risk settings, guide infection prevention and control strategies as well as to assess their efficacy.

In Northern Cyprus, data on the frequency and trends of antimicrobial susceptibility among MRSA isolates circulating in the hospital setting is very limited. This study aims to screen for the frequency and antibiotic resistance patterns of MRSA in a central hospital in Northern Cyprus, in order to provide susceptibility data to guide clinical practice along with decision making, and implementation of management and prevention policies.

MATERIAL and METHOD

Study area and study design

This study was performed at Near East University Hospital in Northern Cyprus. This hospital has 500 inpatient beds and serves about 146,000 outpatients and 6,500 inpatients; approximately 3,000 surgeries are performed annually. The hospital has 33-bed intensive care capacity with the distribution of 14 beds for general intensive care, 14 beds for coronary intensive care, three beds for cardiovascular surgery intensive care and two beds for pediatric intensive care.

A total of 449 *S. aureus* isolated from clinical samples of patients admitted to the Microbiology Laboratory at Near East University Hospital from

January 2016 to December 2020 were included in this study. Patient data such as age, gender, hospital department and admission type were electronically stored. The clinical samples included aspiration fluid, blood, abscess/wound, urine, sputum, nasal/throat swab, catheter tip, bronchoalveolar lavage and pleural fluid. The samples were cultured on blood agar and EMB agar, and were incubated aerobically at 35°C for 24-48 hours. Repeating isolates from the patients were omitted from the study.

Identification and antibiotic susceptibility testing

Identification of isolates and antimicrobial susceptibility testing have been performed by Vitek-2 automated identification and susceptibility testing system (bioMérieux, France). Antibiotic susceptibility was assessed according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints (23). Bacterial cultures grown on agar media were suspended in sterile saline at McFarland 0.45-0.55 and were consequently inoculated into Vitek-2 panels as per manufacturer's recommendations. Antimicrobial susceptibility of each isolate to ciprofloxacin, cefoxitin, clindamycin, daptomycin, erythromycin, gentamicin, levofloxacin, linezolid, nitrofurantoin, penicillin G, teicoplanin, tetracycline, trimethoprim/sulfamethoxazole and vancomycin was recorded. Methicillin resistance was assessed using the disc diffusion method with cefoxitin (30µg) (Bioanalyse, Turkey) on Mueller-Hinton agar (Difco, Becton Dickinson, USA) plates. Cefoxitin susceptibility was assessed with EUCAST guidelines and MRSA diagnosis was performed with cefoxitin disc/MIC results.

Multi-drug resistance (MDR4) was defined as beta-lactam resistance plus nonsusceptibility (inducible, intermediate or high-level resistance) to any three additional classes of antimicrobial drug including fluoroquinolones, tetracyclines, macrolides, aminoglycosides, oxazolidinones, glycopeptides, lipopeptides, sulfonamides and ansamycins (24).

Data analysis

All collected data was imported into SPSS Software version 23.0 (IBM Corp., Armonk N.Y., USA) and statistical analysis was performed using Pearson Chi Square, Fisher's Exact Test and One-Way ANOVA test. A p value <0.05 was considered as statistically significant.

The study was approved by the Near East University Scientific Researches Ethics Committee (Date: 26.11.2020 and Number: 2020/85-1190).

RESULTS

Socio-demographic characteristics

In this study, a total of 449 *S. aureus* clinical isolates from patients admitted to the hospital between January 2016 to December 2020 were analyzed. Among the patients, 57.2% (257/449) were male and 42.8% (192/449) were female. The mean patient age was 51.36±25.70. There was no statistically significant association between the mean age of male and female patients and *S. aureus* infection (p = 0.998).

Frequency of *S. aureus* and MRSA

The number of *S. aureus* isolates was detected to be 78 in 2016, 105 in 2017, 89 in 2018, 76 in 2019 and 101 in 2020. The frequency of MRSA in 2016-2020 are given in Table 1. The number of staphylococcal infections was higher in inpatient care (n=268, 59.7%) compared to outpatients (n=181, 40.3%). The distribution of inpatients and outpatients according to year is given in Table 1. The highest rates of *S. aureus* isolates were recorded in the cardiology (n=75, 16.7%) followed by dermatology (n=59, 13.10%), and infectious disease (n=57, 12.7%) among all departments within the hospital for all the years evaluated (Figure 1a). Infection by *S. aureus* were most frequently found in abscess/would (n=174, 38.8%), followed by aspiration fluids (n=77, 17.1%) and blood (n=77, 17.1%) specimens (Fig. 1b). A higher frequency of MSSA (n=55, 20.6%) was observed in bloodstream infections compared to MRSA (n=22, 12.1%) (Table 2).

Table 1. Distribution of MRSA isolates according to gender, year, admission type and seasons

	MRSA (n, %)	MSSA (n, %)	*p-value*
Gender			
Male	99 (54.4)	158 (59.3)	0.315
Female	83 (45.6)	109 (40.8)	
Year			
2016	38 (48.7)	40 (51.3)	< 0.001*
2017	44 (41.9)	61 (58.1)	
2018	15 (16.9)	74 (83.1)	
2019	33 (43.4)	43 (56.6)	
2020	52 (51.5)	49 (48.5)	
Admission			
Inpatient	125 (46.6)	143 (53.4)	0.001*
Outpatient	57 (31.5)	124 (68.5)	
Season			
Spring	49 (43.0)	65 (57.0)	0.550
Summer	42 (41.6)	59 (58.4)	
Autumn	54 (42.5)	73 (57.5)	
Winter	37 (34.6)	70 (65.4)	

* statistically significant

Table 2. Distribution of sample type according to methicillin resistance in *S. aureus*

	MRSA (n, %)	MSSA (n, %)
Abscess/wound	56 (30.8)	118 (44.2)
Urethral/vaginal swab	10 (5.5)	16 (6.0)
Pleural Fluid	1 (0.6)	1 (0.4)
Nasal/throat swab	14 (7.7)	7 (2.6)
Aspiration fluid	39 (21.4)	38 (14.2)
Sputum	15 (8.2)	9 (3.4)
Urine	17 (9.3)	18 (6.7)
Blood	22 (12.1)	55 (20.6)
Catheter tip	5 (2.7)	4 (1.5)
Bronchoalveolar lavage	3 (1.6)	1 (0.4)

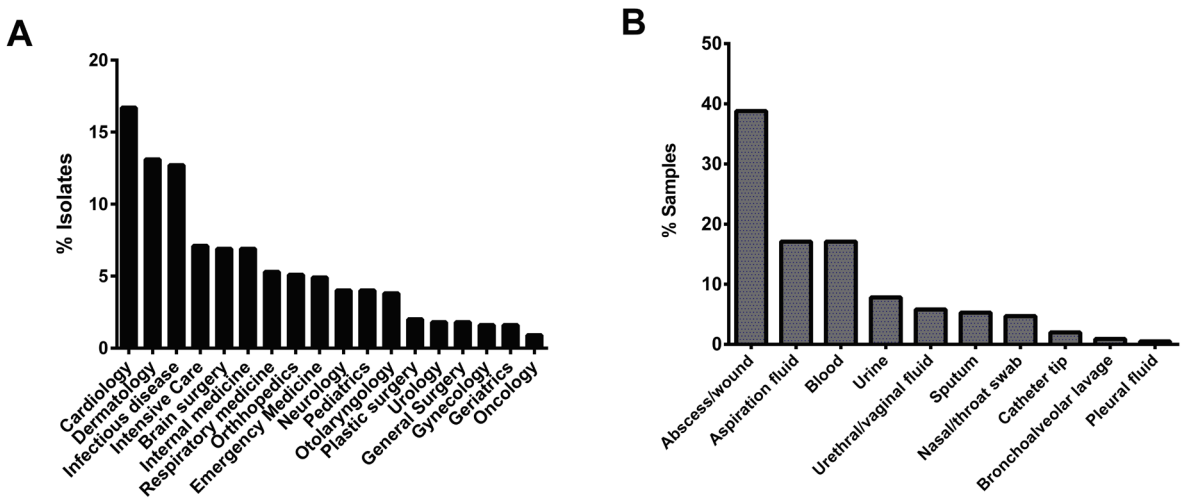

Figure 1. Distribution of *S. aureus* isolates according to a) hospital departments and b) sample source

Distribution and risk factors for MRSA colonization

Among the *S. aureus* isolates collected in 2016-2020, the frequency of MRSA was 40.5% (n=182), whereas MSSA was observed in 59.5% (n=267) of the samples (p <0.001). Over the 5-year period evaluated, the frequency of MRSA was highest in 2020 (n=52, 51.1%) which was statistically higher than previous years (n=38, 48.7% in 2016, n=44, 41.9% in 2017, n=15, 16.9% in 2018, n=33, 43.4% in 2019) (p < 0.001). Inpatients had statistically higher rates of MRSA infections (n=125, 46.6%) compared to outpatients (n=57, 31.5%) (p = 0.001). Of 182 MRSA isolated, 99 (54.4%) were males and 83 (45.6%) were females (Table 1). No statistically significant association between gender and MRSA infection was observed (p = 0.315). Patient age was between 0 and 96 with an average of 57.07±24.61. Importantly, the mean age of patients with MRSA infection was statistically higher than those with MSSA infections (p < 0.001; mean age: 57.07±24.61 and 47.47±25.74, respectively). Rates of MRSA infections were similar in different seasons (p = 0.550).

Antimicrobial susceptibility patterns of *S. aureus*

Among the tested antibiotics, *S. aureus* isolates were most resistant to erythromycin (39.5%, n=136/344), followed by tetracycline (35.4%, n=155/438), clindamycin (25.8%, n=114/442), ciprofloxacin (14.6%, n=61/418), levofloxacin (11.8%, n=52/443), trimethoprim/sulfamethoxazole (9.9%, n=42/422), fusidic acid (8.1%, n=14/174), rifampin (6.9%, n=17/248), fosfomycin (6.8%, n=11/163) and tobramycin (5.6%, n=13/232). On the contrary, high susceptibility rates were detected in all *S. aureus* tested for vancomycin (98.9%), daptomycin (98.9%), linezolid (98.8%), teicoplanin (97.3%) and gentamicin (96.8%) (Table 3). Antibiotic susceptibility testing of MRSA isolates revealed statistically higher resistance levels towards ciprofloxacin, clindamycin, erythromycin, tetracycline, levofloxacin, fosfomycin, tobramycin and rifampin compared to MSSA isolates.

Multi-drug resistance of the isolates was also evaluated. MRSA isolates resistant to beta-lactams plus three additional antimicrobial classes were classified as multidrug resistant (MDR4). Overall, fifty-six (30.8%) of the isolates were multi-drug resistant in 2016-2020 period. The distribution of MDR isolates was observed to vary among years with the lowest rate (5.8%, n=3/52) detected in 2020 as shown in Figure 2. Overall, the rate of MDR MRSA was observed to significantly decrease in the post-pandemic period (p=0.0001) compared to the

pre-pandemic period (55.3% in 2016, 36.4% in 2017, 26.7% in 2018, 36.4% in 2019). MDR phenotype was found to be at similar rates in men (32.3%, n=32/99) and women (28.9%, n=24/83) with no statistical difference among gender. There was no statistically significant difference among MDR isolates isolated from inpatients and outpatients (p = 0.852).

Table 3. Antibiotic resistance profiles (%) of MRSA and MSSA isolates to different antimicrobial agents between 2016-2020

Antibiotic	MRSA (%)	MSSA (%)	p-value
Erythromycin	85.4	11.7	< 0.001*
Tetracycline	68.0	13.7	< 0.001*
Clindamycin	52.9	8.2	< 0.001*
Ciprofloxacin	23.8	8.7	< 0.001*
Levofloxacin	19.8	6.4	< 0.001*
Fosfomycin	13.0	1.2	< 0.005*
Rifampicin	12.0	4.2	< 0.05*
Trimethoprim/sulfamethoxazole	11.6	8.9	0.372
Tobramycin	11.1	3.1	<0.05*
Fusidic acid	7.3	8.7	0.739
Gentamicin	5.2	2.0	0.074
Teicoplanin	3.4	1.5	0.166
Linezolid	2.3	0.4	0.086
Vancomycin	1.6	0.7	0.326
Daptomycin	1.5	0.9	0.484

* statistically significant

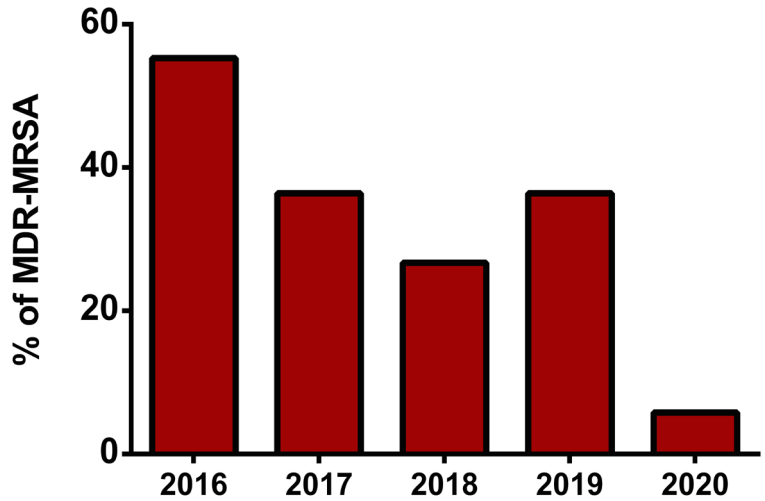

Figure 2. Rates of MDR-MRSA in 2016-2020 period

DISCUSSION

MRSA is an important pathogen in healthcare (25-27). In Northern Cyprus, an analysis of MRSA infections and associated risk factors at a local scale are scarce. This is the first study to document the frequency as well as antimicrobial and multi-drug resistance profiles of MRSA and MSSA in Northern Cyprus.

One of the significant observations over the five-year study period was the higher rates of MSSA observed compared to MRSA isolates (59.5% vs 40.5%) ($p < 0.001$). The European Antimicrobial Resistance Surveillance Network data between 2015 and 2018 documented a frequency of MRSA as high as 38.4% in Cyprus (27). Our observations indicate a higher MRSA rate in 2016-2020 period. Compared to the EU/EEA population-weighted mean percentage of MRSA as 17.4% in 2014, our findings show higher rates of MRSA in the study period in the hospital setting in Northern Cyprus. In the current study, from 2016 to 2020, although fluctuating, the overall MRSA trend was shown to be significantly higher in 2020 (51.49%) compared with previous years, with a drop (16.85%) in 2018. Evidence from previous studies show that proportion of MRSA among *S. aureus* isolates is variable. Although general trend in frequency has been shown to increase previously (29), some studies have reported declining rates. MRSA has declined in England (30,31) and the USA (32,33).

With respect to patients demographics, evidence from several studies indicated a greater proportion of *S. aureus* infections among male and older age groups (34,35). Our results show a significant age-specific trend associated to MRSA frequency, and although it was not statistically significant, the gender-specific trend observed was consistent with previous reports in the literature (36-38).

In general, clinical samples of wound/abscess suggestive of staphylococcal SSTI are the most common isolates recovered (39). In this study, regardless of the methicillin resistance in *S. aureus*, sources indicative of SSTIs (wound/abscess) and invasive infections (blood, aspiration fluid) were more commonly observed. This finding is in agreement with previous reports indicating the frequency of MRSA and MSSA isolated from these sources to be predominant compared to other clinical sources (35,40). However, regarding bloodstream infections, a higher frequency of MSSA was observed in our study. Such trend was also described in previously conducted studies focusing on risk factors for *S. aureus* infections (41, 42). Conversely, Wi et al and Hindy et al have reported a significant predominance of MRSA associated bacteremia (43,44). Although we have found overall more MSSA cases in the study population, inpatients were at significantly higher risk to develop MRSA infections. Inpatients care status has been associated with longer hospital stay, thus prolonged exposure to medical procedures and increased likelihood to develop MRSA infections (45). Similarly, Lakhundi et al. (46) reported hospital length of stay, old age and invasive medical procedures as risk factors for MRSA infections.

Several factors such as seasonal fluctuation contribute to spatial and temporal occurrence of infectious diseases (47). Conversely to many studies that have demonstrated a strong and consistent link between seasons and MRSA incidence rate, the examination of MRSA rates over our study period showed no statistically significant correlation. In 2017, Psoter and colleagues reported a predominance of MRSA related respiratory infections during winter season (48). Another study depicted a periodicity pattern in MRSA peak and antibiotic consumption; the latter occurring several month after the first was detected (49). It appears that seasonality incidence of MRSA, more than following a simple meteorological pattern, is a multifactorial mechanism (50).

Susceptibility of MRSA isolates investigated in this study was reported to be over 90% for daptomycin, vancomycin, linezolid, teicoplanin, gentamicin and fusidic acid. One study reported similar rate of susceptibility; yet, conversely to their report, MRSA isolates were found to be slightly less susceptible

to rifampicin and trimethoprim/sulfamethoxazole in the current study (51). A significantly decreased susceptibility for antibiotics such as erythromycin, clindamycin, ciprofloxacin, tetracycline, levofloxacin, fosfomycin in MRSA was observed. Similar trends were reported in 2017, in which MRSA were found to be highly resistant to erythromycin, clindamycin, ciprofloxacin compared to MSSA, and regardless of the clinical source (38). Total susceptibility to vancomycin and rifampicin (52) and gentamicin (38) were also noted in literature. In the current study, MDR4 MRSA rates were observed to decrease in 2020 compared to previous years, which can be attributable to the decrease in antibiotic consumption mostly in the primary care sector and may be the result of a decrease in the number of primary care consultations, either because of hesitancy to seek healthcare for mild self-limiting infections, or difficulties in obtaining an appointment for a consultation during the pandemic. It is likely that this has resulted in fewer antibiotic prescriptions for mild and self-limiting infections, and has had a more noticeable effect in countries where overuse and inappropriate use was common before the COVID-19 pandemic.

In conclusion; this five-year study presents the frequency and antibiotic resistance profiles of MRSA and MSSA isolates at a central hospital in Northern Cyprus. An alarmingly high rate of MRSA infections in older patients is reported. MRSA isolates were found to have increased resistance to several antibiotics. Given the fast-paced evolution of MRSA epidemiology, constant monitoring of alterations in incidence and resistance patterns is critical for the timely adjustment of local control and prevention strategies.

LIMITATIONS OF THE STUDY

This study is single-centered therefore does not represent the overall antimicrobial susceptibility patterns of *S. aureus* in the region. The vancomycin, linezolid and teicoplanin resistance observed in MRSA isolates was not validated due to the lack of a reference laboratory in Northern Cyprus. In addition, identification of antibiotic resistance genes with molecular methods is lacking. Future multi-centered studies with molecular characterization of isolates would give an overview of the antibiotic resistance patterns across the country would be beneficial.

ETHICS COMMITTEE APPROVAL

* The study was approved by the Near East University Scientific Researches Ethics Committee (Date: 26.11.2020 and Number: 2020/85-1190).

CONFLICT OF INTEREST

The author declares no conflict of interest.

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