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Nasal *Staphylococcus* Colonization in Nursing Home Residents and Antibiotic Resistance Profiles

Huzurevi Sakinlerinde Nazal *Staphylococcus* Kolonizasyonu ve Antibiyotik Direnç Profilleri

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Abstract

Introduction: Staphylococci are microorganisms that are resistant to many antibiotics. *Staphylococcus epidermidis* is a normal flora bacterium that has recently emerged as a nosocomial pathogen and has become a worldwide issue. The aim of the study was to determine the prevalence of coagulase negative staphylococci, *Staphylococcus aureus* nasal carriage, and antibiotic resistance of these bacteria in nursing home residents.
Materials and Methods: This study was conducted in July 2017. Forty-six samples obtained from the nasal mucosa of the participants were cultured. The species identification was done by MALDI-TOF-MS. Disk diffusion was applied to determine the antibiotic susceptibility of isolates, and polymerase chain reaction assay was employed to identify the known antimicrobial resistance genes.
Results: Staphylococci were isolated from 28 (61%) of the 46 residents. The isolates (n=29) were *S. epidermidis* (n=22), *Staphylococcus succinus* (n=4), and *S. aureus* (n=3). Two different strains of *S. epidermidis* were isolated from one participant. While methicillin-resistant *S. aureus* was not identified in isolates; Methicillin-resistant *S. epidermidis* (MRSE) was found in 43% (n=12). In addition, 68% of *S. epidermidis* strains were multidrug resistant (MDR) (to at least one agent in three or more antimicrobial groups other than β-lactams). All methicillin-resistant *S. epidermidis* (MRSE) isolates were mecA positive. Among the MRSE isolates (n=12), the following resistance genes were found: *blaZ* (n=5), *lnuA* (n=1),*tetK* (n=1), *ermA* (n=1), *aac(6')/aph*(2'') (n=1), and *ant*(4')-*Ia* (n=1).
Conclusion: To our knowledge, multi-drug resistant MRSE was detected in nursing home residents for the first time in Turkey with this study. This result suggests that *S. epidermidis* could serve as a reservoir of drug resistance by persistent colonization in the nasal mucosa. Observation and molecular surveillance could be applied to limit the spread of such resistant nosocomial pathogens.
Keywords: Nursing home, PCR, *Staphylococcus epidermidis*, nasal flora

Öz

Giriş: Stafilokoklar, birçok antibiyotiğe dirençli mikroorganizmalardır. *Staphylococcus epidermidis*, son zamanlarda nozokomiyal bir patojen olarak ortaya çıkan ve dünya çapında sorun haline gelen bir normal flora bakterisidir. Bu çalışmanın amacı, huzurevi sakinlerinde koagülaz negatif stafilokoklar ve *Staphylococcus aureus*'un nazal taşıyıcılık prevalansını ve bu bakterilerin antibiyotik direncini belirlemekti.
Gereç ve Yöntem: Bu çalışma Temmuz 2017'de yapıldı. Katılımcıların burun mukozasından alınan 46 örneğin kültürü yapıldı. Tür tanımlaması MALDI-TOF-MS ile yapıldı. İzolatların antibiyotik duyarlılığını belirlemek için disk difüzyon testi uygulandı ve bilinen antimikrobiyal direnç genlerini belirlemek için polimeraz zincir reaksiyon yöntemi kullanıldı.
Bulgular: Kırkaltı katılımcının 28'inden (%61) stafilokok izole edildi. İzolatlar (n=29) *S. epidermidis* (n=22), *Staphylococcus succinus* (n=4) ve *S. aureus* (n=3) idi. Bir katılımcıdan iki farklı *S. epidermidis* suşu izole edildi. İzolatlarda, metisiline dirençli *S. aureus* izole edilmezken; %43'ünde (n=12) metisiline dirençli *S. epidermidis* (MRSE) bulundu. *S. epidermidis* suşlarının %68'i çok ilaca (β-laktamlar dışındaki üç veya daha fazla antimikrobiyal gruptaki en az bir ajana) dirençliydi. Tüm MRSE izolatları *mecA* pozitifti. MRSE izolatları (n=12) arasında *blaZ* (n=5), *lnuA* (n=1), *tetK* (n=1), *ermA* (n=1), *aac*(6')/*aph*(2'') (n=1) ve *ant*(4')-*Ia* (n=1) direnç genleri bulundu.

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Sonuç: Bildiğimiz kadarıyla, bu araştırmayla Türkiye'de ilk kez huzurevinde yaşayanlarda çok ilaca dirençli MRSE tespit edilmiştir. Sonuçlarımız, *S. epidermidis*'in nazal mukozada kalıcı kolonizasyon yoluyla bir ilaç direnci rezervuarı görevi görebileceğini düşündürmektedir. Bu dirençli hastane patojeninin yayılması moleküler sürveyans yoluyla gözlemlenmeli ve sınırlandırılmalıdır.
Anahtar Kelimeler: Huzurevi, PCR, *Staphylococcus epidermidis*, nazal flora

Introduction

Staphylococci are members of normal flora, commonly found in the skin and mucosal membranes. Studies have shown the presence of staphylococcal population in anterior nares as normal bacterial flora at a density of 10^3-10^6 CFU/cm^2[1]. The presence of staphylococci, especially *Staphylococcus epidermidis*, in the nose prevents the settlement of many pathogens in the nasal mucosa[2,3]. However, despite this benefit, it may also emerge as an important opportunistic pathogen in the immunocompromised hosts[4,5]. In addition to the aforementioned information, *S. epidermidis* has evolved into an extraordinary nosocomial pathogen known as "superbug" published in *Nature* and is important[6]. Moreover, because *S. epidermidis* is thought to be a potential reservoir of resistance genes for some pathogenic bacteria such as *S. aureus*, this reservoir may spread methicillin-resistant *S. aureus* (MRSA). The nasal carriers of staphylococci may be a risk factor for nosocomial and community-acquired staphylococcal infections because it serves as a reservoir from which bacteria can spread when the host's defenses are compromised. The persistence of these bacteria during the treatment of these infections may result in the emergence and spread of antibiotic-resistant strains. Treatment options for methicillin-resistant staphylococci infections are relatively limited and have resulted in the administration of non-β-lactam antibiotics[6-8].

In the case of *S. epidermidis*-related infections, antibiotic selection differs depending on the factors, in addition to antimicrobial resistance, such as clinical picture and location of the infection. *S. epidermidis* strains causing nosocomial infections tend to show multidrug-resistant characteristics including methicillin resistance. Although vancomycin-resistant strains have been reported, vancomycin remains the drug of choice in many *S. epidermidis* infections. Antibiotic combinations containing rifampicin have also been recommended for the treatment of staphylococcal biofilm infections. Daptomycin, linezolid, quinupristin/dalfopristin, and tigecycline have also been used to treat these infections[8-11].

The staphylococcal cassette chromosome *mec* (SCC*mec*), which contains the *mecA* gene, encodes methicillin resistance. Some methicillin-resistant staphylococci containing SCC*mec* may spread without antibiotic pressure. In some cases, *S. epidermidis* may transmit mobile genetic elements and drug-resistance genes to *S. aureus*[2].

Staphylococci may cause various infections that have severe clinical pictures such as sepsis, soft tissue infections, and pneumonia in those with impaired immune systems[13]. Methicillin-resistant staphylococci, frequently encountered in hospital infections, can be also isolated from community-acquired infections, which are infections acquired outside the hospitals. However, nosocomial infections are acquired while receiving any kind of healthcare, which can occur in various settings, including hospitals, long-term care facilities, and ambulatory settings, and they can also appear after discharge. Healthcare-associated infections (HAIs) can also include occupational infections that affect employees[12].

Nasal carriage of methicillin-resistant staphylococci has been reported, especially in public areas including schools, hospitals, dorm rooms, and nursing homes, where inadequate hygiene conditions are present. Methicillin-resistant staphylococci found in the nasal mucosa may be spread by contaminated hands, droplets, airborne dust, and inanimate materials. Nursing homes are an ideal environment for the transmission and spread of methicillin-resistant *Staphylococci* among older persons living in that place. Therefore, to prevent the development and possible complications of Methicillin-resistant staphylococci (MRS) infections, which may pose a high risk and potential mortality in older individuals[14], it is crucial to know and follow the nasal MRS carriage in older people living in nursing homes[15]. Thus, this study aimed to investigate the prevalence of the nasal carriage of methicillin-resistant staphylococci in the nasal mucosa of nursing home residents. Additionally, phenotypic and genotypic antibiotic resistance patterns were examined.

Materials and Methods

Sampling

This study was conducted in a nursing home in southern Turkey in July 2017. There were 188 individuals in the nursing homes. A total of 118 (65 women, 53 men) and 70 people were at the rehabilitation and non-rehabilitation units, respectively. Of the 188 residents, 46 (11 from the rehabilitation unit) signed the consent form and agreed to participate in the study. In addition to the acceptance to participate in this study, participants who could speak Turkish, were not mentally retarded, and could give verbal consent without hearing or speaking disabilities were considered. The samples were obtained from the anterior nares of the volunteers after a short instruction was provided and informed consent was obtained.

Isolation and Identification of Staphylococcal Isolates

The swabs were enriched in Mueller-Hinton broth containing 6.5% NaCl overnight at 37 °C. An aliquot of this suspension was plated on Mueller-Hinton agar plates containing 2% sodium chloride with/without 0.25 mg/L oxacillin and incubated overnight at 37 °C. Suspected colonies were subcultured, and species were identified using Matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) (MALDI Biotype, MA, USA)[16].

Antimicrobial Susceptibility Testing

The Kirby-Bauer disk diffusion method was used to test the sensitivity to 13 antimicrobial agents. The antimicrobials tested were penicillin, erythromycin, ampicillin, oxacillin, sulfamethoxazole-trimethoprim, gentamicin, tetracycline, clindamycin, chloramphenicol, amoxicillin-clavulanate, ciprofloxacin, and rifampin. The results were assessed according to the Clinical and Laboratory Standards Institute criteria[17]. For all species, the methicillin-resistant phenotype of strains was assessed based on the OXA results. Furthermore, according to previously standardized criteria, all isolates resistant to three or more antimicrobial classes other than β-lactams have been classified as multi-drug resistant (MDR)[15,18].

Detection of Resistance Genes

Genotypic antimicrobial resistance genes were investigated by the polymerase chain reaction assay. The resistance genes of oxacillin/methicillin, β-lactamase, aminoglycoside, macrolide (erythromycin)-lincosamide-streptogramin B, and tetracycline were *mecA*, *blaZ*, *aac(6')/aph(2'')*, *ant(4')-Ia*, *aph(3')-IIIa*, *ermA*, *lnuA*, and *tetK*, respectively[19-22].

Oligonucleotide primers and thermal cycles for all primers examined are summarized in Tables 1 and 2. The PCR results were analyzed on a 1.5% agarose gel and additionally controlled by sequencing.

Ethics Committee Approval

This study was approved by the Ethical Committee of the Medical Faculty of Hatay Mustafa Kemal University (protocol no: 2017-123, date: 13.07.2017).

Results

The median age of the 46 participants was 78 (range 62-98) years (α=8.6), 17.3% were male, and 82.7% were female. The most common diseases were diabetes mellitus, 46% (21/46); orthopedic disorders, 11% (5/46); decubitus, 4% (2/46); heart diseases, 26% (12/46); asthma, 22% (10/46); hypertension, 52% (24/46), and psychological and neurological diseases, 15% (7/46). Of the nursing home residents, 38 (83%) have a chronic disease. Moreover, 118 and 70 residents were at the rehabilitation and non-rehabilitation units, respectively. Within the last year, five had a history of admission to the hospital, and four had a history of antibiotic use.

Staphylococcal strains were detected in 28 (61%) of the 46 nursing home residents. A total of 29 staphylococci isolates were obtained from these 28 participants. These were isolates of *S. epidermidis* (22/29; 75%) *S. succinus* (4/29; 14%), and *S. aureus* (3/29; 11%). In one sample, two colonies with different morphologies were isolated, and they were both identified as *S. epidermidis*, indicating the likely contamination of this person with two strains.

Table 1. Oligonucleotide primers used in the study

Primer	Target gene	Primer sequence 5'-3'	Fragment size (bp)	References
aac(6')/aph(2')	*aac(6')/aph(2')* F *aac(6')/aph(2')* R	GAAGTACGCAGAAGAGA CATGGCAAGCTCTAGGA	491	Choi et al.[19]
aph(3')-IIIa	*aph(3')-IIIa* F *aph(3')-IIIa* R	AAATACCGCTGCGTA CATACTCTTCCGAGCAA	242	Choi et al.[19]
ant(4')-Ia	*ant(4')-Ia* F *ant(4')-Ia* R	AATCGGTAGAAGCCCAA GCACCTGCCATTGCTA	135	Choi et al.[19]
mecA	*mecA* F *mecA* R	CCTAGTAAAGCTCCGGAA CTAGTCCATTCGGTCCA	314	Choi et al.[19]
blaZ	*blaZ* F *blaZ* R	TAAGAGATTTGCCTATGCTT AATTCCTTCATTACACTCTTGG	635	Olsen et al.[21]
tetK	*tetK* F *tetK* R	GTA GCG ACA ATA GGT AAT AGT GTA GTG ACA ATA AAC CTC CTA	360	Strommenger et al.[20]
ermA	*ermA* F *ermA* R	AAG CGG TAA ACC CCT CTG A AAG CGG TAA ACC CCT CTG A	190	Strommenger et al.[20]
lnuA	*lnuA* F *lnuA* R	GGTGGCTGGGGGGTAGATGTATTAACTGG GCTTCTTTTGAAATACATGGTATTTTTCGA TC	323	Lina et al.[22]

Table 2. Thermal cycles for the three primers used in the study

No	Step	mecA	blaZ	*aac(6′)/aph(2′)*	aph(3′)-IIIa
1	Initial denaturation	95 °C 5 min	95 °C 5 min	95 °C 5 min	95 °C 5 min
2	Denaturation	95 °C 2 min	94 °C 1 min	95 °C 2 min	95 °C 2 min
	Annealing	58 °C 30 s (30 cycles)	54 °C 1 min (35 cycles)	58 °C 30 s (30 cycles)	58 °C 30 s (30 cycles)
	Extension	72 °C 30 s	72 °C 1 min	72 °C 30 s	72 °C 30 s
3	Final extension	72 °C 7 min	72 °C 10 min	72 °C 10 min	72 °C 10 min
4	Keeping	+4 °C ∞	+4 °C ∞	+4 °C ∞	+4 °C ∞
No	Step	lnuA	ermA	tetK	*ant(4′)-Ia*
1	Initial denaturation	95 °C 5 min	94 °C 3 min		94 °C 3 min 95 °C 5 min
2	Denaturation	94 °C 2 min	94 °C 30 s	94 °C 30 s	95 °C 2 min
	Annealing	57 °C 30 s (30 cycles)	55 °C 30 s (30 cycles)	55 °C 30 s (30 cycles)	58 °C 30 s (30 cycles)
	Extension	72 °C 1 min	72 °C 30 s	72 °C 30 s	72 °C 30 s
3	Final extension	72 °C 7 min	72 °C 4 min		72 °C 4 min 72 °C 10 min
4	Keeping	+4 °C ∞	+4 °C ∞		+4 °C ∞ +4 °C ∞

Table 3. Comparison of mecA and MR-CoNS rates in our study with some studies in the literature

References	Number of MRSE	Year	Prevalence of mecA n (%)
Present study	28	2017	12/28 (43%)
Marincola et al.[33]	117	2021	9/117 (7%)
Budri et al.[34]	137	2018	18/137 (13.1%)
	Number of cases	Year	Prevalence of MR-CoNS n (%)
Present study	46	2017	12/28 (43%)
Ruppé et al.[37]	330 Algeria	2008	66/330 (20%)
	338 Mali		27/338 (8%)
	448 Moldova		54/448 (12%)
	442 Cambodia		93/442 (21%)
Kateete et al.[38]	513		122/513 (23.8%)
Lebeaux et al.[39]	154	212	78/154 (50.6%)
Widerström et al.[36]	124	2011	2/124 (1.6%)
Cavanagh et al.[35]	386	2016	16/386 (4.1%)

MRSE: Methicillin-resistant *S. epidermidis*, MR-CoNS: Methicillin-resistant-coagulase-negative staphylococci

Antimicrobial Susceptibility

The resistance rates of *S. epidermidis* and *S. aureus* against some antibiotics are summarized in Figure 1. All *Staphylococcus* isolates were susceptible to quinupristin/dalfopristin, amoxicillin/clavulanate, and chloramphenicol. Compared with *S. aureus*, MRSE strains were more resistant to many antimicrobial agents, particularly erythromycin. Additionally, 68% of the *S. epidermidis* strains were MDR. In addition, *S. aureus* had a higher (100%) level of ciprofloxacin resistance.

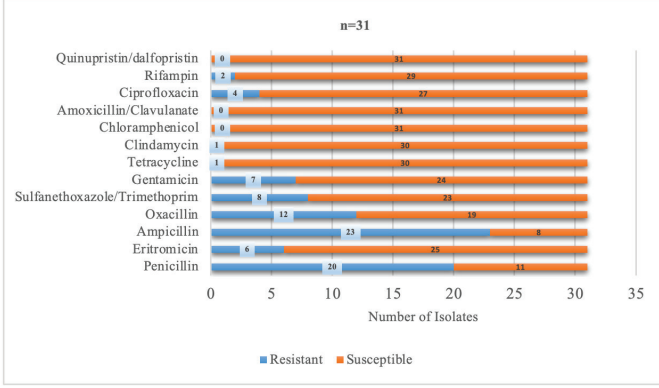

Figure 1. Staphylococci resistance profiles assessed by agar disk diffusion

Molecular Analysis

While MRSE was determined in 43% (12/28) of the nursing home residents, no MRSA was detected. Interestingly, among the 11 samples obtained from those in the rehabilitation unit, 10 were found to be MRSE-positive. All MRSE isolates (n=12) possessed the *mecA* gene. Five also had the *blaZ* gene, whereas *lnuA*, *tetK*, *ermA*, *aac(6′)/aph(2″)*, and *ant(4′)-Ia* were detected in one isolate. The *blaZ* gene was present in all *S. aureus* (methicillin-susceptible staphylococci) isolates, whereas the *aac(6′)/aph(2″)* gene was present in two isolates. The most frequently isolated genes were the *blaZ* gene, at a rate of 54% (15/28), followed by the *mecA* gene, with a rate of 43% (12/28) (Figures 2, 3).

Discussion

Knowledge of the subspecies and characteristics of staphylococci, especially those obtained from the nasal mucosa of the older residents, at a rate of 6-38%, is important[23-29]. Therefore, many studies have investigated the presence of *S. aureus* and its drug

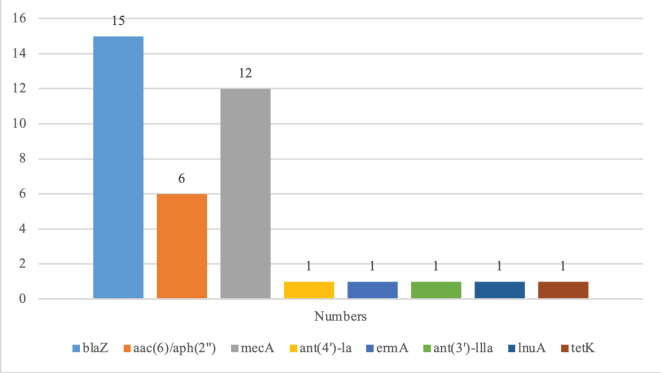

Figure 2. Incidence of antibiotic resistance genes in a staphylococci isolate

resistance in the nasal mucosa of nursing home residents in Turkey and worldwide. However, the study findings are novel as the high rate of *S. epidermidis* carriage among nursing home residents was first time shown in this study. *S. epidermidis* nasal carriage could be important, particularly in older people with chronic diseases. *S. epidermidis* could also transfer its drug resistance traits to other bacteria[2].

Studies conducted in Turkey have shown 5-40.8% contamination level for MRSA in the nasal cavity of older people[30,31]. In addition, in a study conducted in 10 nursing homes in Malta, the MRSA carriage rate was between 0% and 25%[13]. However, we could not detect MRSA strain in the present study, which could be attributed to the low number of participants tested or to the province's local situation.

On the contrary, a high rate (43%) of nasal carriage was found for MRSE in nursing home residents. In the present study, one participant was contaminated with two *S. epidermidis* strains, potentially different clone, because of the different colony morphologies and different antibiotic resistance profiles. *S. epidermidis* could gain some extra antimicrobial resistance genes in any niche, resulting in different antimicrobial resistance profiles and even different colony morphologies. However, this assumption should be proved by molecular assays (such as whole-genome sequencing of plasmids, cgMLST, etc.). However, further characterization steps are quite difficult and expensive. Accordingly, these two isolates are of two different strains in the light of current evidence based on colony morphology and different antimicrobial resistance profile. In addition, MRSE carriage is higher in bedridden (90%) participants. In addition, the rate of hospitalization or antimicrobial agent administration in the past year was lower in coagulase-negative staphylococci (CoNS)+ residents than in *S. aureus* (+) residents. This result indicated that MRSEs isolated from the participants were community-acquired, not hospital-acquired MRSEs. The fact that most of the MRSE-positive participants are bedridden and need care suggests that it can be transmitted through

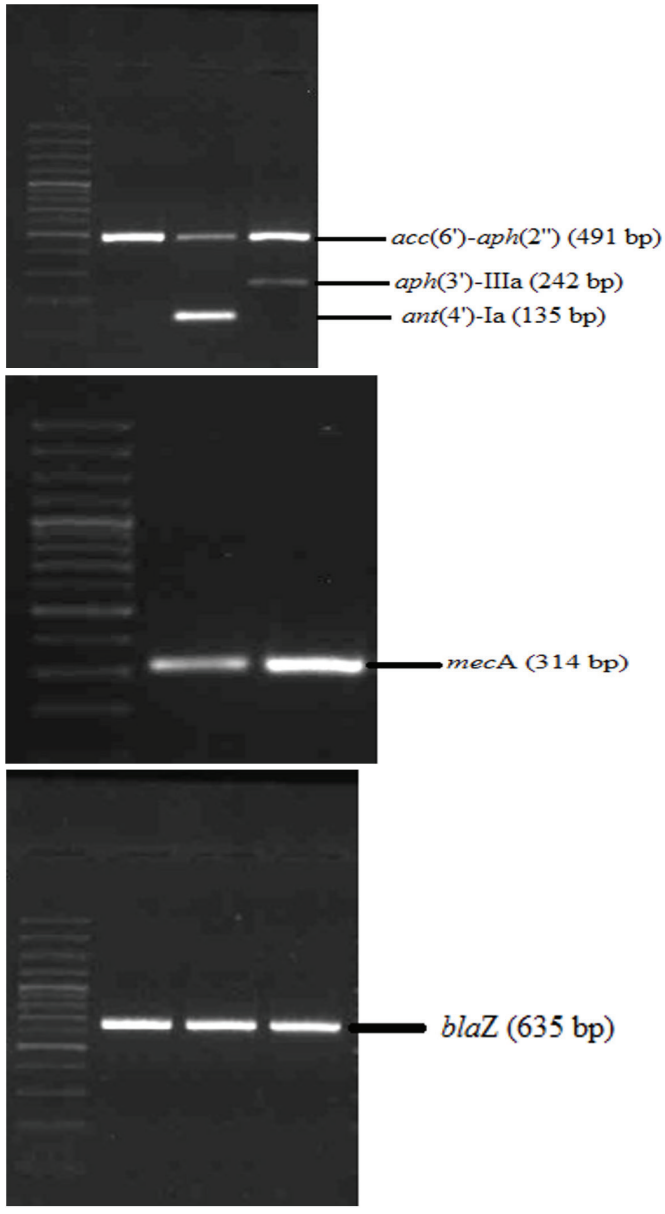

Figure 3. Agarose gel electrophoresis images of polymerase chain reaction amplification products of aac(6')-aph(2''), aph(3')-IIIa, ant(4')-Ia and mecA, and blaZ

care personnel. However, the lack of results of nasal carriage in this personnel is one of the study limitations, which will be investigated in the next study. We could not find any study investigating the nasal carriage of MRSE in nursing home residents, to which we could compare our results in terms of MRSE. Therefore, we compared our findings with studies investigating the prevalence of MRSE in other parts of society, such as medical students and doctors. Several studies involving medical students and medical doctors have reported 2.5-23.5% nasal carriage rates of MRSE[1,6,32]. Higuchi reported that the nasal carriage rate of MRSE in medical students was 23.5%[1]. In another study conducted in Austria, the nasal carriage rate

in medical students was 2.5%[32]. The age of the participants in our study may have contributed to the higher MRSE rates in our study than in the aforementioned studies.

The frequency of the *mecA* gene in CoNS isolates in our study was higher (43%) than in that in community-based studies conducted in Europe (7%, 13%)[33,34]. However, in studies conducted in Uganda, Algeria, Mali, Moldova, and Cambodia, MR-CoNS rates ranged from 16% to 50%, comparable to the 43% MR-ConS rate in our study (Table 3)[35-39].

In the present study, more than 50% of isolated staphylococci were resistant to many antibiotics. *S. epidermidis*, besides oxacillin, exhibited more resistance to antimicrobial agents such as erythromycin, ampicillin, and penicillin. Moreover, 74% of the isolated staphylococci were resistant to ampicillin, 65% to penicillin, and 39% to oxacillin. Kasela et al.[15] reported that staphylococci obtained from nursing homes in Poland had higher rates of resistance to the antibiotics tested in our study. They also stated that all staphylococci isolated from the nasal mucosa (100%, n=21) were resistant to penicillin and oxacillin. Because β-lactams are the most frequently prescribed antibiotics for outpatient treatment, they may be the reason for widespread β-lactam resistance worldwide.

In this study, 68% of the *S. epidermidis* strains were MDR. The MDR bacteria are challenging to treat in nosocomial and community-acquired infections. The choice of vancomycin for the empirical treatment of methicillin-resistant isolates may result in the emergence of MDR strains[40,41]. The emergence of the MDR bacteria, such as vancomycin-resistant staphylococci and vancomycin-resistant enterococci (VRE), has increased with exposure to vancomycin. Vancomycin-resistant staphylococci and VRE may also be resistant to many antibiotics[42]. Furthermore, vancomycin should not be used in the empirical treatment of Methicillin-sensitive staphylococcus (MSS). Although vancomycin is one of the first-line drugs in the treatment of MRS infections, it is not the first choice in the treatment of MSS infections, and its effectiveness in these infections is not optimal. Consequently, this situation may prolong the treatment process and increase the risk of developing resistance to other drugs, including vancomycin[41].

In the present study, 39% of staphylococci were MDR, which was lower than that reported by de Benito et al.[6]. In addition, we found that 68% of the *S. epidermidis* strains were MDR.

Methicillin/oxacillin resistance is a significant characteristic of staphylococci. It is primarily encoded by the *mecA* gene located on a large genomic island known as SCC*mec*. The SCCmec element, harboring resistance or virulence genes to different antibiotic groups or classes, is a mobile genetic element that can spread between different staphylococcal species[41]. Therefore, *mecA* carriage may be a marker for MDR isolates. Based on this information, the *mecA* gene was found in 50% of the CoNS isolates, higher than that in studies conducted on community-acquired CoNS[33,34].

In the present study, no significant relationship was found between the presence of chronic diseases and the nasal carriage of methicillin-resistant staphylococci. The methicillin-resistant staphylococcal nasal carriage may be important in nursing home residents aged >65 years, whose immune system functions have begun to decline.

Study Limitations

As research strengths, this study was conducted in a nursing home, where there is close contact among the older population with chronic diseases. However, this study has some limitations. First, we did not attempt to obtain oropharyngeal samples to improve our results. Second, the sample did not include employers from the nursing home, and the number of participants was limited. Finally, the participants were not compared with the older population outside the nursing home. To our knowledge, no similar study has been conducted in our country to which we can compare our MRSE results.

Conclusion

This study showed that nursing homes can be an important reservoir for community-associated MRSE. However, the primary risk factor for nasal MRSE carriage could not be defined given the small number of study participants. Our findings indicate that the presence of MDR-CoNS isolates in the community has reached an alarming point. Moreover, community-acquired MDR-CoNS bacteria, besides their recognized role in reservoir resistance genes for the more pathogenic *S. aureus*, may pose a risk as opportunistic pathogens for older individuals when such strains spread to the environment and hospitals.

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Ethics

Ethics Committee Approval: This study was approved by the Ethical Committee of the Medical Faculty of Hatay Mustafa Kemal University (protocol no: 2017-123, date: 13.07.2017).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.Ö.G., P.D.G., Concept: C.Ö.G., P.D.G., Design: C.Ö.G., P.D.G., Data Collection or Processing:

C.Ö.G., P.D.G., Analysis or Interpretation: C.Ö.G., Ö.A., Literature Search: C.Ö.G., Ö.A., Writing: C.Ö.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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