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Identification and Macrolide-Lincosamide-Streptogramin B Resistance Phenotypes and Biofilm Formation of Coagulase-Negative Staphylococci Strains Isolated from Bloodstream infections in Türkiye

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What is already known on this topic?

- *Coagulase-negative staphylococci (CoNS) are part of the normal human microbiota but have emerged as significant pathogens, especially in immunocompromised patients.*
- *The increasing use of indwelling medical devices has led to a rise in CoNS-related bloodstream infections, with Staphylococcus epidermidis being the most commonly isolated species.*
- *Biofilm formation is a crucial virulence factor in CoNS, contributing to antibiotic resistance and persistent infections.*

What this study adds on this topic?

- *Biofilm formation was observed in 73% of the most prevalent CoNS strains, with significantly higher rates in MRCoNS (S. epidermidis: 77%, S. hominis: 79%, S. haemolyticus: 92%), confirming the association between methicillin resistance and biofilm production.*
- *Inducible MLSB (iMLSB) resistance was detected in 36% of MRCoNS and 8% of MSCoNS isolates, emphasizing the need for routine D-test screening to prevent treatment failure with clindamycin.*
- *This study reinforces the necessity for effective antimicrobial stewardship and infection control measures, given the high prevalence of multidrug-resistant and biofilm-forming CoNS strains in bloodstream infections.*

Abstract

Objective: This study aimed to determine the species, biofilm formation ability, and macrolide-lincosamide-streptogramin B (MLSB) resistance phenotypes of coagulase-negative staphylococci (CoNS) isolated from blood cultures.

Methods: Three hundred CoNS strains isolated from blood samples of patients with bacteremia hospitalized in intensive care units and other services in the hospital between 2020 and 2023 were retrospectively evaluated. Blood cultures were analyzed using the Bactec-9120 system. Strains were identified using MALDI-TOF MS (Bruker Daltonics, Germany). Antimicrobial susceptibilities were determined using the Kirby–Bauer disc diffusion method on Mueller–Hinton agar and evaluated according to EUCAST standards. Biofilm formation was assessed by the Congo Red Agar method.

Results: Among isolates, *Staphylococcus epidermidis* was the most prevalent species (57.6%; $P < .05$). Methicillin-resistant CoNS isolates (MRCoNS) were determined to be more resistant to antibiotics than methicillin-susceptible CoNS isolates (MSCoNS) ($P < .001$). None of the isolates were resistant to vancomycin, teicoplanin, and linezolid. A total of 222 MRCoNS isolates were phenotypically categorized as the inducible MLSB, constitutive MLSB, and efflux type resistance were determined in 36%, 9%, and 36% and in 78 MSCoNS isolates 8%, 15%, and 38%, respectively. Methicillin-resistant CoNS exhibited significantly higher biofilm formation rates (77%) compared to methicillin-susceptible isolates ($P < .001$).

Conclusion: The results showed that *S. epidermidis* is the most common CoNS species isolated in bloodstream infections. Multidrug resistance and increased biofilm formation ability, which come with increasing methicillin resistance, can lead to infections that are difficult to treat. It is important to routinely determine the resistance status of these bacteria for effective antibiotic therapy and prevention of nosocomial infections.

Keywords: Biofilm formation, bloodstream infections, coagulase-negative Staphylococci, macrolide-lincosamide-streptogramin B, *Staphylococcus epidermidis*

Introduction

Coagulase-negative staphylococci (CoNS), once considered contaminants, are now frequently identified as the causative agents of nosocomial infections, especially *Staphylococcus epidermidis*, due to the increased use of indwelling medical devices.[1-3]

Invasive procedures that allow bacteria to enter the body, a weakened immune system, and the use of antibiotics that suppress the microbiota have further contributed to the growing clinical significance of CoNS.[4,5]

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The ability to form biofilm is the most important virulence factor of *S. epidermidis*.[6,7] Bacteria in biofilm form are resistant to antibiotics, and much research has focused on the role of biofilm forms of bacteria in increasing antibiotic resistance and the mechanisms that cause this.[7,8]

Multidrug-resistant (MDR) isolates, which emerged as a result of methicillin resistance, complicate the treatment and control of staphylococcal infections.[9-11] Macrolide resistance in staphylococcal strains develops by ribosomal modification or active pump.[12] Macrolide-lincosamide-streptogramin B (MLSB) group antibiotics are agents used in staphylococcal infections and act by inhibiting protein synthesis. Since all 3 groups of drugs use the same binding site, a mutation developing here results in resistance to 3 different antibiotics (MLSB resistance).[13]

Macrolide-lincosamide-streptogramin B resistance is mediated by methylase enzymes encoded by erm genes (mainly ermA, ermB, and ermC). Macrolide-lincosamide-streptogramin B resistance can be inducible (iMLSB) or constitutive (cMLSB).[14] Inducible resistance develops in the presence of methylase inducers such as erythromycin (ERY) or azithromycin. The strains are resistant to ERY but sensitive to clindamycin.[15] Investigating inducible resistance to clindamycin, which is widely used in the treatment of staphylococcal infections, is important in preventing treatment failure.[15,16] In strains showing inducible MLSB resistance, antagonism of clindamycin by ERY can be demonstrated by induction tests such as double disc synergy or D-test. In contrast, strains with cMLSB resistance are resistant to both groups of antibiotics.[16] Macrolide resistance may also develop with the pump system (M phenotype) depending on the presence of the *mef* gene. Resistance developed in this way is called macrolide-streptogramin B (MSB) resistance and this type of resistance is associated with the *msrA* gene in staphylococci. The MsrA-positive strains are completely susceptible to clindamycin because this antibiotic is not an inducer or substrate for the pump.[15] The third resistance mechanism is drug inactivation (L-type) and is based on the production of enzymes that inactivate antibiotics.[17] Enzymatic inactivation provides resistance only to structural antibiotics. Erythromycin-sensitive but clindamycin-resistant isolates should also be considered.[18]

The aim of this study was to determine the antibiotic resistance patterns, MLSB-type resistance phenotypes and biofilm formation of CoNS isolated from blood cultures of hospitalized patients with bacteremia.

Methods

Collection

Strains obtained from 300 blood samples taken from patients who were followed up with the diagnosis of bacteremia at İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine hospital between 2020 and 2023 were examined. 240 (80%) patients between the ages of 1 and 92 were hospitalized in internal medicine wards, and 60 (20%) patients were hospitalized in intensive care units. Only patients with at least 2 positive blood cultures were included, and contaminated strains were excluded. Ethics committee approval was received for this study from the Ethics Committee of İstanbul Medipol University (Approval no: E-10840098-202.3.02-6677, Date: November 11, 2024). Written informed consent was obtained from patients who participated in this study.

Bacterial Isolation and Identification

Blood samples from patients were inoculated into blood culture vials and incubated in the Bactec™ 9120 (Becton Dickinson) automated blood culture system. Samples with a positive signal were inoculated on 5% sheep blood agar, chocolate agar, and MacConkey agar plates. They were evaluated after an incubation period of 24-48 hours at 35°C. Bacteria with catalase-positive, Gram-positive cocci morphology were identified using the Phoenix automated system (BD Diagnostic Systems, Sparks, MD). The identification results were confirmed by MALDI-TOF MS (Bruker Daltonics).

Antibiotic Susceptibility Test

Antimicrobial resistance for strains was determined by the Kirby–Bauer disk diffusion method using the following antibiotics and evaluated according to EUCAST criteria: ERY, ciprofloxacin, trimethoprim-sulfamethoxazole, clindamycin, gentamicin, tetracycline, rifampicin, teicoplanin, linezolid, and vancomycin.[19]

Identification of Macrolide-Lincosamide-Streptogramin B Phenotypes

Macrolide-lincosamide-streptogramin B phenotypes were identified by D-test with erythromycin (ERY; 15 µg) and clindamycin (C; 2 µg) discs applied at 15 mm intervals on Mueller–Hinton agar. After a 24 hour incubation period at 35°C, a flattening zone of inhibition adjacent to the ERY disc indicated the inducible type (D-shaped zone) of MLSB resistance (iMLSB), while resistance to both ERY and C was termed the constitutive type (cMLSB) (Figure 1). The absence of a D-shaped zone in ERY-resistant and C-sensitive strains was interpreted as the efflux phenotype.

Biofilm Formation

The Congo red-agar (CRA) method was selected for the qualitative assessment of biofilms in CoNS strains.[14] Black colonies were considered strong biofilm producers, while red colonies were considered non-biofilm producers (Figure 2). While the CRA method provides a practical assessment of biofilm formation, its qualitative nature is a limitation compared to quantitative techniques such

Figure 1. D-test positive results on Mueller–Hinton agar.

Figure 2. Congo red-agar method for biofilm formation.

as crystal violet staining in microtiter plate assays. Future studies should consider incorporating these methods for a more comprehensive analysis.

Statistical Analysis

Statistical analysis was performed using IBM Statistical Package for Social Sciences software (version 22.0; IBM SPSS Corp.; Armonk, NY, USA). Antibiotic susceptibility profiles, MLSB phenotypes, and biofilm formation rates were compared for MR-CoNS and MS-CoNS and expressed as percentages. A chi-square test was used to assess the association between 2 groups of categorical variables. A *P*-value ≤ .05 was considered statistically significant. Confidence intervals for resistance rates are shown in Table 1 to enhance the clarity and interpretability of the results.

Results

Among 300 CoNS isolates, *S. epidermidis* was the most prevalent species (57.6%; *P* < .05) followed by *Staphylococcus hominis* (22%), *Staphylococcus haemolyticus* (13%), *Staphylococcus capitis* (3%), *Staphylococcus saprophyticus* (1%), *Staphylococcus cohnii* (1%), *Staphylococcus lugdunensis* (1%), *Staphylococcus warneri* (0.6%), *Staphylococcus schleiferi* (0.3%), and *Staphylococcus pettenkoferi* (0.3%) (Figure 3).

The rate of resistance to methicillin was 74%. Methicillin-resistant CoNS isolates were determined to be more resistant to antibiotics than MSCoNS isolates (*P* < .001). Strains (100%) were found susceptible to teicoplanin, vancomycin, and linezolid. Resistance rates of MRCoNS and MSCoNS isolates to the antibacterial agents, respectively, were as follows: gentamicin 48% and 11%, ERY 81% and 61%, clindamycin 45% and 23%, trimethoprim-sulfamethoxazole 56% and 19%, ciprofloxacin 69% and 20%, tetracycline 44% and 19%, and rifampicin 37% and 3% (Table 1; Figure 4).

The iMLSB, cMLSB, and efflux type (MSB) resistance were determined in 36%, 9%, and 36% of MRCoNS and in 8%, 15%, and 38% of MSCoNS, respectively (Table 2; Figure 5).

Table 1. Antibiotic Resistance Rates of MRCoNS and MSCoNS Strains

Antibiotcs	Total (n = 300) n (%)	MRCoNS (n = 222) n (%)	MRCoNS (%) (95% CI)	MSCoNS (n = 78)	MSCoNS (%) (95% CI)	*P*
Erythromycin	227 (75.6)	179 (80.6)	80.6 (74.9-85.3)	48 (61.5)	61.5 (50.4-71.6)	.001*
Ciprofloxacin	169 (56.3)	153 (69.9)	69.9 (62.6-74.6)	16 (20.5)	20.5 (13.0-30.8)	<.001*
Trimethoprim-Sulfamethoxazole	140 (46.6)	125 (56.3)	56.3 (49.7-62.7)	15 (19.2)	19.2 (12.0-29.3)	<.001*
Clindamycin	119 (39.6)	101 (45.4)	45.4 (39.1-52.1)	18 (23)	23.0 (15.1-33.6)	<.001*
Gentamicin	115 (38.3)	106 (47.7)	47.7 (41.3-54.3)	9 (11.5)	11.5 (6.2-20.5)	<.001*
Tetracycline	113 (37.6)	98 (44.1)	44.1 (37.8-50.7)	15 (19.2)	19.2 (12.0-29.3)	<.001*
Rifampicin	84 (28)	82 (36.9)	36.9 (30.9-43.5)	2 (2.56)	2.56 (0.7-8.9)	<.001*
Teicoplanin	0 (0)	0 (0)	–	0 (0)		NA
Linezolid	0 (0)	0 (0)	–	0 (0)		NA
Vancomycin	0 (0)	0 (0)	–	0 (0)		NA

The resistance rates of MRCoNS to erythromycin and ciprofloxacin were 80.6% (95% CI: 74.9-85.3) and 69.9% (95% CI: 62.6-74.6), respectively, while rates for MSCoNS were significantly lower at 61.5% (95% CI: 50.4-71.6) and 20.5% (95% CI: 13.0-30.8) (*P* < .001). The resistance rates of MRCoNS to trimethoprim-sulfamethoxazole and clindamycin were 56.3% (95% CI: 49.7-62.7) and 45.4% (95% CI: 39.1-52.1), respectively, while rates for MSCoNS were significantly lower at 19.2% (95% CI: 12.0-29.3) and 23.0% (95% CI: 15.1-33.6) (*P* < .001). The resistance rates of MRCoNS to gentamicin and tetracycline were 47.7% (95% CI: 41.3-54.3) and 44.1% (95% CI: 37.8-50.7), respectively, while rates for MSCoNS were significantly lower at 11.5% (95% CI: 6.2-20.5) and 19.2% (95% CI: 12.0-29.3) (*P* < .001). The resistance rate of MRCoNS to rifampicin was 36.9% (95% CI: 30.9-43.5), while the rate for MSCoNS was significantly lower at 2.56% (95% CI: 0.7-8.9) (*P* < .001). No resistance to teicoplanin, linezolid, or vancomycin was observed in either MRCoNS or MSCoNS isolates.
MRCoNS, methicillin-resistant CoNS; MSCoNS: methicillin-susceptible CoNS; NA, not applicable.
*Chi-square was conducted between the resistance rates for the MR-CoNS and MS-CoNS strains. *P*-value ≤ .05 was statistically significant.

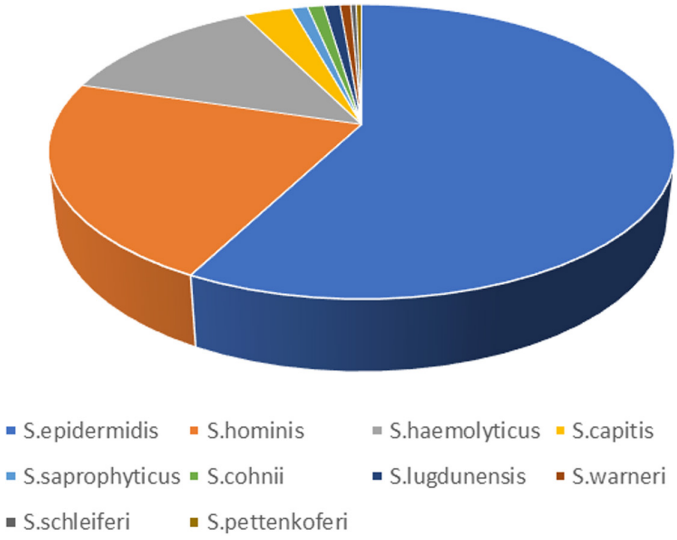

Figure 3. Distribution of the 300 CoNS strains.

Among all CoNS, *S. epidermidis*, *S. hominis*, and *S. haemolyticus* were the top 3 prevalent strains with 29 (93%). In methicillin-resistant *S. epidermidis*, *S. hominis*, *S. haemolyticus* strains, resistance phenotypes are presented in Table 3 with details.

Biofilm formation ability was found to be 73% (202) in the top-3 prevalent strains of CoNS. Biofilm formation rates and methicillin resistance rates by species are presented in Table 4.

Discussion

Cagulase-negative staphylococcis are typically nonpathogenic organisms that reside in the human skin and mucosal microbiota. However, with the growing use of prosthetic devices and medical instruments, these bacteria have become significant pathogens, particularly in catheter-related and bloodstream infections, especially in immunocompromised individuals.[20]

In this study, 300 CoNS strains isolated from blood samples of patients diagnosed with bloodstream infections were analyzed. The predominant strain isolated was *S. epidermidis* (57.6%), followed by *S. hominis* (22%) and *S. haemolyticus* (13%). Similar studies conducted in Türkiye have reported the prevalence of *S. epidermidis* strains isolated from clinical samples to range between 44% and 51%, followed by *S. hominis* and *S. haemolyticus*, respectively.[21-23]

Table 2. Distribution of MLSB Phenotypes Among MRCoNS and MSCoNS Strains

	MRCoNS (n = 222)	MSCoNS (n = 78)	Total (n = 300)	
Phenotypes	**n (%)**	**n (%)**	**n (%)**	***P***
MLSB	80 (36)	6 (8)	86 (28.6)	<.001*
cMLSB	19 (9)	12 (15)	31 (10.3)	.137
MSB	80 (36)	30 (38)	110 (36.6)	.702
L-type	2 (0.9)	0 (0)	2 (0.6)	1
S-type	41 (18)	30 (38)	71 (23.6)	.001*
Total	222 (100)	78 (100)	300 (100)	

The strain distribution found in this study was consistent with these reported data. The ability of bacteria to form biofilms is thought to play an important role in the suppression of antibiotics and the immune system.[24] In this study, the ability to form biofilm was determined as 74% in *S. epidermidis* strains, 70% in *S. hominis* strains, and 70% in *S. haemolyticus* strains. Biofilm formation rates were higher in methicillin-resistant strains: 77% in *S. epidermidis*, 79% in *S. hominis* strains, and 92% in *S. haemolyticus* strains.

The biofilm formation rates observed in MRCoNS (77%) align with global findings where methicillin resistance is a strong predictor of biofilm formation. This association underscores the need for targeted therapeutic strategies to disrupt biofilms and combat resistance.[25]

Similar studies have reported that methicillin-resistant *S. epidermidis* strains cause device-related infections due to their biofilm production potential.[26,27] The findings suggest the problems that biofilm-forming strains may pose in the treatment of nosocomial infections.

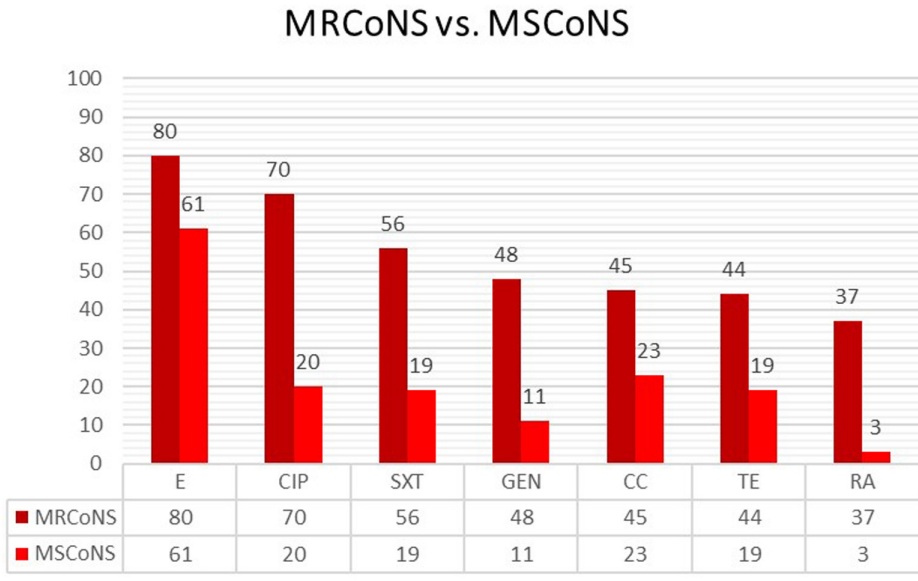

Figure 4. Comparison of antimicrobial resistance rates of MRCoNS and MSCoNS strains. CC, clindamycin; CIP, ciprofloxacin; E, erythromycin; GEN, gentamycin; RA, rifampicin; SXT, trimethoprim-sulfamethoxazole; TE, tetracycline.

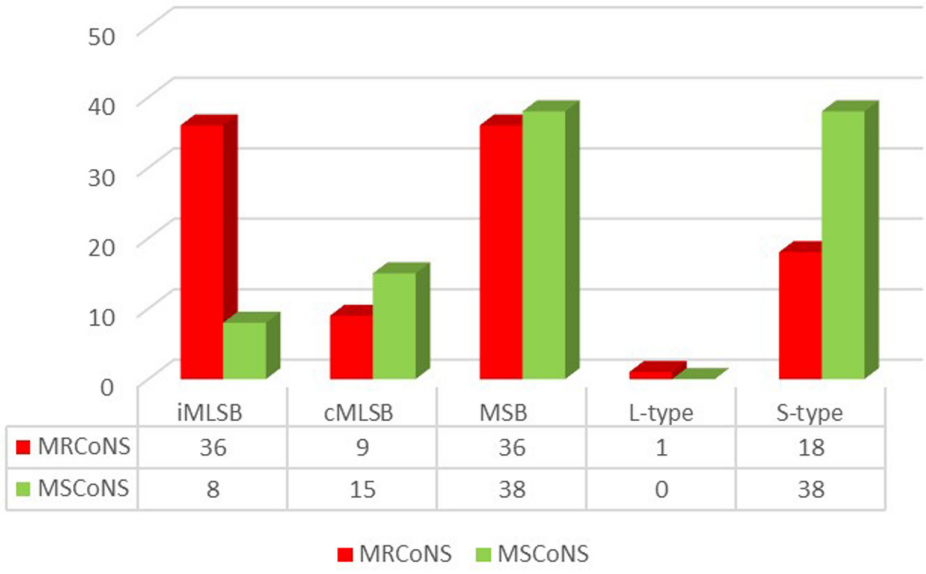

Figure 5. Resistance phenotype rates of the MRCoNS, MSCoNS strains.

Multidrug resistance seen in methicillin-resistant staphylococci has become an important health problem that reduces the treatment success of staphylococcal infections and increases the mortality and morbidity of patients.[28-31] Methicillin resistance was detected at 74%. Antimicrobial susceptibility patterns of methicillin resistant *S. epidermidis* strains showed a high level of resistance as follows: 81%, 56%, 44%, 45%, 48%, 37%, 69% for ERY, trimethoprim-sulfamethoxazole, tetracycline, clindamycin, gentamicin, rifampicin, and ciprofloxacin, respectively. In a similar study, it was reported that the methicillin resistance rate in *S. epidermidis* strains was 86%, and 39% of these strains were resistant to at least 4 antibiotics.[29] Mirzaei et al[32] detected ERY resistance in 80% of the strains they isolated and drew attention to the increase in macrolide resistance. Glycopeptide group antibiotics are used in the treatment of methicillin-resistant staphylococcal infections.[33] However, in recent years, vancomycin and teicoplanin resistance has also been reported in *S. epidermidis*.[29] All strains we tested were sensitive to vancomycin and teicoplanin.

Macrolide-lincosamide-streptogramin B resistance rates vary between countries and even between hospitals in the same country. Recent studies highlight the rising prevalence of MLSB resistance globally, underscoring the need for regional surveillance to inform treatment protocols and antimicrobial stewardship efforts.[25] In this study, iMLSB, cMLSB, and MSB type resistance phenotypes were found to be 36%, 9%, and 36% in MRCoNS strains, and 8%, 15%, and 38% in MSCoNS strains, respectively. Inducible MLSB was found to be 31%, 0%, and 28% in methicillin-resistant *S. epidermidis*, *S. hominis*, and *S. haemolyticus* strains, respectively. Constitutive MLSB was found to be 11%, 22%, and 14%, respectively. The MSB was found to be 31%, 63%, and 56%, respectively. In this study, the most common resistance phenotype was found to be inducible MLSB resistance. Some studies, such as Li et al[34] and Szczuka et al[18] have shown that iMLSB resistance can also be commonly found in *S. haemolyticus* and *S. hominis* species. However, Uyar Güleç et al[35] reported the rates of cMLSB and iMLSB and MSB phenotypes as 30.5%, 18.3%, and 6.1%, respectively, in 28 CoNS strains included in their study. Szemraj et al[36] also observed a high rate of constitutive MLSB resistance type in S. *epidermidis, S. hominis*, and *S. haemolyticus* strains isolated from blood.

The study shows that *S. epidermidis* is the most prevalent CoNS isolated as a causative agent of bloodstream infection in the hospital. *Staphylococcus hominis*, *S. haemolyticus*, *S. capitis*, and *S. saprophyticus* also cause infections at increasing rates. The methicillin

Table 3. Comparative Statistical Analysis of Resistance Phenotypes of the Top 3 Prevalent CoNS with/Without Methicillin Resistance.

	M.R. *S. epidermidis*	M.S. *S. epidermidis*			M.R. *S. hominis*	M.S. *S. hominis*			M.R. *S. haemolyticus*	M.S. *S. haemolyticus*		
Phenotype	**n (%)**	**n (%)**	**n (%)**	***P***	**n (%)**	**n (%)**	**n (%)**	***P***	**n (%)**	**n (%)**	**n (%)**	***P***
iMLSB	38 (31)	0 (0)	38	<.001	0 (0)	0 (0)	0	NA	10 (28)	0 (0)	10	.035
cMLSB	13 (11)	1 (2)	14	.068	11 (22)	0 (0)	11	.035	5 (14)	0 (0)	5	.323
MSB	38 (31)	24 (47)	62	.069	32 (63)	7 (50)	39	.111	20 (56)	0 (0)	20	.005
L-type	4 (3)	6 (12)	10	.066	0 (0)	0 (0)	0	NA	0 (0)	0 (0)	0	NA
S-type	29 (24)	20 (39)	49	.061	8 (16)	7 (50)	15	.144	1 (3)	3 (100)	4	.077
Total	**122 (100)**	**51 (100)**	**173**		**51 (100)**	**14 (100)**	**65**		**36 (100)**	**3 (100)**	**39**	

*Chi-square was conducted between the resistance rates for the MR and MS strains. *P*-value ≤ .05 was statistically significant.

Table 4. Relationship Between Biofilm Formation and Methicillin Resistance in the Top 3 Prevalent CoNS Strains

	Biofilm Producers	Non-Biofilm Producers	*P*
S. epidermidis	128/173	45/173	.310
Methicillin resistant *S. epidermidis*	99/122	23/122	
S. hominis	47/66	19/66	.876
Methicillin resistant *S. hominis*	37/51	14/51	
S. haemolyticus	27/39	12/39	1
Methicillin resistant *S. haemolyticus*	25/36	11/36	

resistance rate is 74%, while iMLSB resistance was found to be 36% in methicillin-resistant strains, and this rate was determined to be 8% in methicillin-susceptible strains ($P < .005$). In this study, a high rate of methicillin resistance (80%) was detected in biofilm-forming strains.

These findings highlight the importance of routine surveillance of MLSB resistance phenotypes and biofilm formation in CoNS isolates. Implementation of stricter infection control measures, coupled with biofilm-targeted therapies, could mitigate the impact of these MDR pathogens in nosocomial settings.[37] Routine screening for methicillin resistance and MLSB phenotypes, combined with efforts to prevent biofilm formation, is critical for optimizing treatment protocols and controlling the spread of MDR CoNS. Future studies should focus on developing biofilm-disrupting agents and exploring the genetic basis of resistance phenotypes in diverse clinical settings.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of İstanbul Medipol University (Approval no: E-10840098-202.3.02-6677, Date: November 11, 2024).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.Ö., O.A., F.K.Ç.; Design – S.Ö., O.A., F.K.Ç.; Supervision – F.K.Ç.; Resources – S.Ö., O.A., F.K.Ç.; Materials – S.Ö., O.A., F.K.Ç.; Data Collection and/or Processing – S.Ö., O.A.; Analysis and/or Interpretation – S.Ö., O.A., F.K.Ç.; Literature Search – S.Ö., O.A.; Writing Manuscript – S.Ö., O.A., F.K.Ç.; Critical Review – F.K.Ç.; Other – S.Ö., O.A., F.K.Ç.

Declaration of Interests: The authors have no conflict of interest to declare.

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