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RESEARCH ARTICLE

Antimicrobial Resistance Profiling of Coagulase-Negative Staphylococci in a Referral Center in South Italy: A Surveillance Study

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Abstract:

Background:

CoNS are part of the normal flora of the skin, upper respiratory tract and human intestine. CoNS are able to colonize host tissues or inert materials such as prosthetics, heart valves, pacemakers, and urinary and venous catheters. They can also internalize in host cells, thus eluding immune defenses and attack by antibiotics.

Objective:

In this study, we collected the epidemiological data and determined the antibiotic susceptibility of 828 CoNS, collected in Garibaldi Hospital (Catania, Italy) between January 2016 and October 2018.

Methods:

Strains were evaluated by determining the Minimum Inhibitory Concentration (MIC) using the broth microdilution method, according to the guidelines of the Clinical and Laboratory Standards Institute. The antibiotic sensitivity pattern of CoNS against eighteen antibiotics was determined.

Results:

For all the 828 clinical isolates, varying resistance rates were observed: ampicillin (87%), penicillin (86%), amoxicillin-clavulanate (71%), oxacillin (70%), erythromycin (69%), azithromycin (68%), levofloxacin (55%), ciprofloxacin (54%), gentamycin (47%), moxifloxacin (42%), trimethoprim-sulfamethoxazole (30%), clindamycin (28%), tetracycline (24%), rifampicin (20%), quinupristin-dalfopristin (synercid) (4%). No strains investigated demonstrated resistance to teicoplanin, vancomycin and linezolid.

Conclusion:

Our results highlight the importance of monitoring the evolution of CoNS resistance in order to implement control measures and reduce the risk of spread in the population.

Keywords: Coagulase-negative staphylococci, Nosocomial pathogens, Epidemiological data, Antimicrobial, Resistance, Virulence factors.

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1. INTRODUCTION

Staphylococci are non-spore-forming bacteria that are widespread in nature. Various species of *Staphylococcus* constitute the normal microbiota of humans and animals: they are found on the skin, on the mucous membranes of the upper respiratory tract and in the intestinal tract. The skin is frequently colonized by staphylococci, especially in humid areas: navel, armpits, groin, perineum, face, hands and scalp. The skin, either intact (through hair follicles or sweat ducts) or interrupted by lesions, represents a frequent entrance for staphylococci. Historically, Coagulase-Negative Staphylococci (CoNS) had been considered to be less pathogenic compared to coagulase-positive ones. However, numerous studies have reported that even coagulase-negative species are equally

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pathogenic [1, 2]. CoNS, as opportunists, are responsible for severe nosocomial and health-care related infections. They are capable of colonizing and infecting humans through different mechanisms, such as adherence, invasion, persistence and evasion of innate and adaptive immunity [3]. *S. epidermidis* is the most commonly isolated CoNS [4 - 7], followed by *S. hominis* [8 - 10], *S. haemolyticus* [11, 12] and *S. capitis* [13 - 15]. *S. lugdunensis* and *S. saprophyticus* are often responsible for septic arthritis [16 - 19] and uncomplicated urinary tract infections [20], respectively. The role of CoNS as pathogens has been demonstrated in human infections, particularly in patients with implanted devices, immunocompromised subjects and preterm infants. Virulence factors of these microorganisms are poorly defined and it is very difficult to determine the pathogenicity of clinical isolates [1]. Furthermore, several CoNS have shown resistance to different antibiotics and the treatment of infections has become very difficult [21 - 23]. Among CoNS, *S. lugdunensis* is the only species susceptible to a wide range of antimicrobials [24]. In addition, there are few recent data in the literature [25 - 28]. Accordingly, the aim of the present study was to investigate the etiology and the antibiotic-resistance profiles of CoNS isolated from hospital environments in South Italy.

2. MATERIALS AND METHODS

2.1. Study Design

The retrospective study was conducted in the National Reference and Specialization Hospitals “Garibaldi” (Catania, Italy) between January 2016 and October 2018. Patient epidemiological data were collected and the identification of bacterial strains provided by the hospital laboratory was confirmed at the Department of Biomedical and Biotechnological Sciences, University of Catania.

2.2. Specimen Collection

All specimens were collected in strict aseptic conditions, according to Guidelines of the Italian National Institute of Health – ISS [29]. Samples were expeditiously transported to the laboratory and processed without undue delay.

2.3. Microbiological Evaluation

Each sample was cultured into Columbia agar plates containing 5% defibrinated horse blood (bioMérieux) and incubated for 18-24 h at 37°C [30]. For *S. lugdunensis* isolation, the incubation time was prolonged (48 h) to obtain visible colonies [31]. Colonies in pure culture were identified by Gram staining, catalase and coagulase tests [32].

2.4. Bacteria Identification and Antimicrobial Susceptibility

Strains identification was performed through the Vitek 2 compact (bioMérieux) system using a GP ID card for Gram-positive bacteria. All the procedures were carried out according to the manufacturer’s instructions. The coagulase-negative *Staphylococcus* species isolated during the study are reported in Table **1**. Antibiotic susceptibility tests were performed by determining the MIC using the broth microdilution method, according to the guidelines of the Clinical and Laboratory Standards Institute [33].

2.5. Statistical Analysis

A Chi-square test was used to study distribution and changes in resistance patterns. Statistical significance was determined if a two-tailed *p*-value was <0.0001.

3. RESULTS

3.1. Distribution of Clinical Isolates

In total, 828 CoNS were isolated from patients admitted to various wards at the hospital. The 828 CoNS isolated belonged to 12 different species (Table **1**), and 89.7% of these strains were isolated from urine, sperm, vaginal swabs, endovascular catheter-associated infections, bladder catheters, blood cultures and bronchial-aspirates (Table **2**). The other 10.3% were isolated from other patient samples (Table **2**). Data analysis showed that the most frequently detected CoNS were *S. haemolyticus*, *S. epidermidis* and *S. hominis*. *S. haemolyticus* was mainly isolated from urine (94/390, 24%), whereas *S. epidermidis* and *S. hominis* were mainly isolated from blood cultures (94/247, 38% and 40/65, 62%, respectively). All other species accounted for only a small portion of the isolates investigated (126/828, 15%) (Table **2**).

3.2. Trends of Antimicrobial Resistance in Coagulase-Negative Staphylococci

The antibiotic susceptibility profiles of CoNS are reported in Table **3**. Of the species investigated, *S. warneri* demonstrated broad antimicrobial susceptibility. The other species showed a similar susceptibility profile except for quinupristin-dalfopristin (synercid). It is noteworthy that *S. epidermidis* and *S. haemolyticus* demonstrated the broadest degree of resistance to the antimicrobials investigated. *S. hominis* and *S. simulans* showed higher resistance to trimethoprim-sulfamethoxazole. Furthermore, elevated resis-tance to rifampicin was found for *S. simulans*, with respect to the other CoNS strains. For all the tested strains, no resistance was found for linezolid, teicoplanin and vancomycin.

Table 1. Coagulase-negative staphylococci isolated during the study.

Species	Number of Isolates	%
Staphylococcus haemolyticus	390	47.1
Staphylococcus epidermidis	247	29.8
Staphylococcus hominis	65	7.8
Staphylococcus warneri	32	3.9
Staphylococcus simulans	29	3.5

(Table 1) cont.....

Species	Number of Isolates	%
Staphylococcus lugdunensis	17	2.1
Staphylococcus capitis	14	1.7
Staphylococcus cohnii	10	1.2
Staphylococcus xylosus	9	1.1
Staphylococcus saprophyticus	6	0.7
Staphylococcus sciuri	5	0.6
Staphylococcus auricularis	4	0.5
TOTAL	**828**	**100**

Table 2. Distribution of coagulase-negative staphylococci in clinical samples.

	Staphylococcus haemolyticus	*Staphylococcus epidermidis*	*Staphylococcus hominis*	*Staphylococcus warneri*	*Staphylococcus simulans*	*Staphylococcus lugdunensis*	*Staphylococcus capitis*	*Staphylococcus cohnii*	*Staphylococcus xylosus*	*Staphylococcus saprophyticus*	*Staphylococcus sciuri*	*Staphylococcus auricularis*
Urine	94 (24%)	-	-	-	5 (17%)	1 (6%)	-	2 (20%)	3 (33%)	4 (67%)	-	-
Sperm	86 (22%)	-	6 (9%)	9 (28%)	4 (14%)	3 (18%)	-	-	-	-	-	-
Vaginal Swabs	66 (17%)	-	-	7 (22%)	2 (7%)	-	-	1 (10%)	-	-	-	-
Hepatic abscess	-	-	-	-	-	1 (6%)	-	-	-	-	-	-
Endovascular catheter-associated infections	27 (7%)	64 (26%)	10 (15%)	3 (9%)	5 (17%)	2 (12%)	-	1 (10%)	-	-	-	-
Cephalorachidian liquor	-	-	-	-	-	1 (5%)	-	-	-	-	-	-
Respiratory tract infections	-	-	-	-	-	9 (53%)	-	-	-	-	5 (100%)	2 (50%)
Soft tissues infections	-	-	-	-	-	-	2 (15%)	-	-	-	-	-
Bladder catheter	-	62 (25%)	3 (5%)	5 (16%)	-	-	-	2 (20%)	-	-	-	-
Septicemia	20 (5%)	-	-	-	-	-	-	-	-	-	-	-
Blood culture	31 (8%)	94 (38%)	40 (62%)	-	9 (32%)	-	-	2 (20%)	2 (23%)	-	-	2 (50%)
Bronchial-aspirate	55 (14%)	22 (9%)	4 (6%)	2 (6%)	1 (1%)	-	-	-	-	2 (33%)	-	-
Skin swabs	11 (3%)	-	-	4 (13%)	2 (10%)	-	4 (25%)	1 (10%)	3 (30%)	-	-	-
Sputum	-	-	-	2 (6%)	-	-	-	-	-	-	-	-
Ocular swabs	-	-	-	-	1 (2%)	-	-	-	-	-	-	-
Nail swabs	-	-	-	-	-	-	-	1 (10%)	1 (14%)	-	-	-
Sepsis	-	-	-	-	-	-	8 (60%)	-	-	-	-	-
Other samples	-	5 (2%)	2 (3%)	-	-	-	-	-	-	-	-	-
TOTAL	**390**	**247**	**65**	**32**	**29**	**17**	**14**	**10**	**9**	**6**	**5**	**4**

Table 3. Antibiotic susceptibility patterns of coagulase-negative staphylococci.

	Staphylococcus haemolyticus			***Staphylococcus epidermidis***			***Staphylococcus hominis***			***Staphylococcus warneri***			***Staphylococcus simulans***			**Other CoNS**		
No. of Isolates	**390**			**247**			**65**			**32**			**29**			**65**		
	S	**I**	**R**	**S**	**I**	**R**	**S**	**I**	**R**	**S**	**I**	**R**	**S**	**I**	**R**	**S**	**I**	**R**
LZD	390 (100%)	-	-	247 (100%)	-	-	65 (100%)	-	-	32 (100%)	-	-	29 (100%)	-	-	65 (100%)	-	-
TEC	386 (99%)	4 (1%)	-	240 (97%)	7 (3%)	-	65 (100%)	-	-	32 (100%)	-	-	28 (97%)	3 (10%)	-	59 (91%)	6 (9%)	-
VAN	382 (98%)	8 (2%)	-	245 (99%)	2 (1%)	-	65 (100%)	-	-	31 (97%)	1 (3%)	-	29 (100%)	-	-	64 (98%)	1 (2%)	-
SYD	370 (95%)	8 (2%)	12 (3%)	225 (91%)	12 (5%)	10 (4%)	64 (99%)	-	1 (1%)	30 (94%)	1 (3%)	1 (3%)	27 (94%)	1 (3%)	1 (3%)	53 (81%)	1 (2%)	11 (17%)
RIF	316 (81%)	8 (2%)	66 (17%)	175 (71%)	3 (1%)	69 (28%)	57 (88%)	1 (1%)	7 (11%)	30 (94%)	-	2 (6%)	18 (62%)	-	11 (38%)	46 (71%)	4 (6%)	15 (23%)
SXT	289 (74%)	-	101 (26%)	180 (73%)	-	67 (27%)	34 (52%)	-	31 (48%)	29 (91%)	-	3 (9%)	17 (59%)	-	12 (41%)	45 (69%)	-	20 (31%)
TET	277 (71%)	23 (6%)	90 (23%)	193 (78%)	2 (1%)	52 (21%)	41 (63%)	3 (5%)	21 (32%)	24 (75%)	-	8 (25%)	22 (76%)	1 (3%)	6 (21%)	41 (63%)	1 (2%)	23 (35%)
CLI	254 (65%)	58 (15%)	78 (20%)	131 (53%)	20 (8%)	96 (39%)	41 (63%)	10 (15%)	14 (22%)	16 (50%)	11 (34%)	5 (16%)	16 (55%)	4 (14%)	9 (31%)	28 (43%)	7 (11%)	30 (46%)
CIP	175 (45%)	12 (3%)	203 (52%)	87 (35%)	7 (3%)	153 (62%)	24 (37%)	2 (3%)	39 (60%)	29 (91%)	1 (3%)	2 (6%)	10 (35%)	1 (3%)	18 (62%)	33 (51%)	6 (9%)	26 (40%)
LVX	168 (43%)	15 (4%)	207 (53%)	84 (34%)	7 (3%)	166 (67%)	22 (34%)	2 (3%)	41 (63%)	28 (88%)	2 (6%)	2 (6%)	10 (34%)	2 (7%)	17 (59%)	22 (34%)	9 (14%)	34 (52%)

(Table 3) cont.....

	Staphylococcus haemolyticus			***Staphylococcus epidermidis***			***Staphylococcus hominis***			***Staphylococcus warneri***			***Staphylococcus simulans***			**Other CoNS**		
No. of Isolates	**390**			**247**			**65**			**32**			**29**			**65**		
	S	**I**	**R**	**S**	**I**	**R**	**S**	**I**	**R**	**S**	**I**	**R**	**S**	**I**	**R**	**S**	**I**	**R**
MXF	160 (41%)	74 (19%)	156 (40%)	82 (33%)	57 (23%)	108 (44%)	19 (29%)	15 (23%)	31 (48%)	27 (84%)	2 (6%)	3 (10%)	10 (35%)	5 (17%)	14 (48%)	17 (26%)	17 (26%)	31 (48%)
GEN	152 (39%)	23 (6%)	215 (55%)	119 (48%)	12 (5%)	116 (47%)	31 (48%)	11 (17%)	23 (35%)	27 (84%)	2 (6%)	3 (10%)	8 (28%)	3 (10%)	18 (62%)	43 (66%)	8 (12%)	14 (22%)
OXA	133 (34%)	-	257 (66%)	44 (18%)	-	203 (82%)	14 (22%)	-	51 (78%)	21 (66%)	-	11 (34%)	6 (21%)	-	23 (79%)	28 (43%)	-	37 (57%)
AMC	129 (33%)	-	261 (67%)	44 (18%)	-	203 (82%)	14 (22%)	-	51 (78%)	22 (69%)	-	10 (31%)	5 (17%)	-	24 (83%)	24 (37%)	-	41 (63%)
AZM	105 (27%)	8 (2%)	277 (71%)	69 (28%)	15 (6%)	163 (66%)	19 (29%)	3 (5%)	43 (66%)	11 (37%)	1 (5%)	20 (63%)	9 (31%)	-	20 (69%)	29 (45%)	-	36 (55%)
ERY	82 (21%)	16 (4%)	292 (75%)	57 (23%)	27 (11%)	163 (66%)	12 (18%)	5 (8%)	48 (74%)	13 (41%)	3 (9%)	16 (50%)	6 (21%)	3 (10%)	20 (69%)	16 (25%)	17 (26%)	32 (49%)
PEN	70 (18%)	-	320 (82%)	10 (4%)	-	237 (96%)	4 (6%)	-	61 (94%)	17 (53%)	-	15 (47%)	1 (3%)	-	28 (97%)	14 (22%)	-	51 (78%)
AMP	66 (17%)	-	324 (83%)	7 (3%)	-	240 (97%)	4 (6%)	-	61 (94%)	17 (53%)	-	15 (47%)	1 (3%)	-	28 (97%)	14 (22%)	-	51 (78%)

Abbreviations: S, susceptible; I, intermediate; R, resistant; LZD, linezolid; TEC, teicoplanin; VAN, vancomycin; SYD, synercid (quinupristin-dalfopristin); RIF, rifampicin; SXT, trimethoprim-sulfamethoxazole; TET, tetracycline; CLI, clindamycin; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; GEN, gentamycin; OXA, oxacillin; AMC, amoxicillin-clavulanate; AZM, azithromycin; ERY, erythromycin; PEN, penicillin; AMP, ampicillin.

4. DISCUSSION

In the last few years, CoNS have emerged as important nosocomial pathogens and are exhibiting increasing virulence and resistance to many antibiotics [34, 35]. In this study, the antibiotic-resistance profiles of CoNS isolated from a hospital environment in South Italy were evaluated. *Staphylococcus haemolyticus* and *Staphylococcus epidermidis* were the most prevalent CoNS isolated from clinical samples. In addition, among the CoNS that were found, we observed differences in antimicrobial resistance. The strains did not exhibit any resistance to linezolid, an oxazolidinone antibacterial agent that inhibits protein synthesis [36]. However, in Italy, plasmidic *cfr*-mediated linezolid resistance has been reported for *S. epidermidis* [37]. No clinical isolate was resistant to the glycopeptides vancomycin and teicoplanin. The high susceptibility rate against these antibiotics could be due to the preferential use of linezolid by hospital clinicians [38]. The first two cases of glycopeptide-resistant CoNS strains were reported by Wilson *et al*. and Schwalbe *et al*. [39, 40]. In a one-year prospective control study conducted in an Italian University Hospital, Tacconelli *et al*. isolated nineteen strains resistant to teicoplanin and one strain resistant to both teicoplanin and vancomycin from 535 subjects with bacteremia. They verified that previous exposure to beta-lactams and glycopeptides, multiple hospitalizations and the concomitant presence of pneumonia were connected with the development of resistance to these antibiotics [41]. In recent years, a worldwide increase in the number of glycopeptide-resistant CoNS has been reported [42]. Sgarabotto *et al*. suggested the association synercid/vancomycin against multidrug-resistant CoNS. The combination of the two antibiotics avoids any side effects [43, 44]. Among the β-lactams, the highest resistance rates were observed for ampicillin and penicillin, followed by amoxicillin-clavulanate, and oxacillin. In Italy, Arciola *et al*. determined the resistance patterns of 15 different species of CoNS isolated from orthopedic implants. The most prevalent species were *S. hominis*, *S. haemolyticus*, *S. capitis*, *S. warneri* and *S. cohnii*, with a resistance rate to penicillin between 51% and 66%. *S. haemolyticus* exhibited high resistance to oxacillin [45]. For the macrolides group, *S. haemolyticus*, *S. epidermidis* and *S. hominis* showed a high rate of erythromycin-resistance [26]. Within the quinolones, resistance to levofloxacin, ciprofloxacin and ofloxacin was found in about 50% of the clinical isolates. Ligozzi *et al*. demonstrated that *norA*-like genes played an important role in the resistance of CoNS to fluoroquinolones [46]. Resistance mechanisms to quinolones include mutations of DNA gyrase and topoisomerase IV [47]. Rifampicin is one of the antibiotics of choice for the treatment of joint and bone infections, due to its ability to penetrate staphylococcal biofilm. The use of this antibiotic has been associated with the development of resistant mutants. Therefore, it is usually administered in association with other antibacterial agents [48]. Trimethoprim-sulfamethoxazole exerts a bacteriostatic effect against staphylococci and susceptibility to this antibiotic combination is highly variable [49]. Regarding tetracycline, in our study, 24% of the strains exhibited resistance. The aminoglycoside gentamycin was tested against CoNS, with a resistance rate of 47%. For the lincosamides class, CoNS showed 28% resistance against clindamycin. Our data are consistent with a recent study by De Vecchi *et al*. [25], where there was a greater antibiotic resistance in *S. haemolyticus* than in *S. capitis* and *S. warneri*. However, it was not possible to compare our results with others obtained in the same geographical area, since any data regarding the frequency of isolation and antibiotic-resistance of coagulase-negative staphylococci in South Italy are available. From our results concerning CoNS resistance, it is possible to state that the antibiotics rifampicin, tetracycline, trimethoprim-sulfameth-oxazole and, to a lesser extent, clindamycin could be used with a good success rate. The antibiotics synercid, linezolid, teicoplanin and vancomycin should be used only in cases where the other antimicrobial agents are not effective.

In the present study, the frequency of isolation and the antibiotic-resistance of coagulase-negative staphylococci from the hospital environment were investigated; not a correlation with the different types of infections. Indeed, since CoNS are commonly present in the human skin and mucous membranes, in some cases, they could contaminate clinical specimens [50, 51]. It is well known that the differentiation between a pathogen and a contaminant is based on several clinical and microbiological factors. Accordingly, in the last few years, different clinical studies have provided guidelines to distinguish pathogenic strains from contaminants, to date, clear, definitive guidelines are still lacking [52]. Although the contamination of specimens is clinically relevant, in this context, we focused on the antibiotic-resistance of coagulase-negative staphylococci isolated from hospital samples. Therefore, we found that, among CoNS, *S. haemolyticus* and *S. epidermidis* are the most frequently isolated bacteria from clinical specimens in a single center in South Italy.

CONCLUSION

The comparative analysis of antibiotic resistance patterns of different CoNS revealed high resistance levels of these strains to the most common antibiotics used in clinical practice. Furthermore, the role of CoNS in the pathogenesis of infection should be assessed for each patient. Different antibiotics, including penicillins, cephalosporins, macrolides, tetracycline and aminoglycosides, have proven to be ineffective against several CoNS species. Hence, there is a need to find new effective antimicrobial drugs. In conclusion, our study could be viewed as the first step of a wider investigation that significantly contributes to the evaluation of the clinical importance of coagulase-negative staphylococci, in a small area of the South of Italy.

LIST OF ABBREVIATIONS

CoNS	=	Coagulase-negative Staphylococci;
MIC	=	Minimum Inhibitory Concentration.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated during the current study are available from the corresponding author on a reasonable request.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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