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Antibiotic resistance patterns of coagulase-negative staphylococcus strains isolated from blood cultures of septicemic patients in Turkey

F. Koksal*, H. Yasar, M. Samasti

Department of Microbiology and Clinical Microbiology, Istanbul University Cerrahpasa Medical Faculty, 34098 Cerrahpasa, Istanbul, Turkey

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Summary

The aim of this study is to determine antibiotic resistance patterns and slime production characteristics of coagulase-negative Staphylococci (CoNS) caused nosocomial bacteremia. A total of 200 CoNS strains were isolated from blood samples of patients with true bacteremia who were hospitalized in intensive care units and in other departments of Istanbul University Cerrahpasa Medical Hospital between 1999 and 2006. Among 200 CoNS isolates, *Staphylococcus epidermidis* was the most prevalent species (87) followed by *Staphylococcus haemolyticus* (23), *Staphylococcus hominis* (19), *Staphylococcus lugdunensis* (18), *Staphylococcus capitis* (15), *Staphylococcus xylosus* (10), *Staphylococcus warneri* (8), *Staphylococcus saprophyticus* (5), *Staphylococcus lentus* (5), *Staphylococcus simulans* (4), *Staphylococcus chromogenes* (3), *Staphylococcus cohnii* (1), *Staphylococcus schleiferi* (1), and *Staphylococcus auricularis* (1). Resistance to methicillin was detected in 67.5% of CoNS isolates. Methicillin-resistant CoNS strains were determined to be more resistant to antibiotics than methicillin-susceptible CoNS strains. Resistance rates of methicillin-resistant and methicillin-susceptible CoNS strains to the antibacterial agents, respectively, were as follows: gentamicin 90% and 17%, erythromycin 80% and 37%, clindamycin 72% and 18%, trimethoprim-sulfamethoxazole 68% and 38%, ciprofloxacin 67% and 23%, tetracycline 60% and 45%, chloramphenicol 56% and 13% and fusidic acid 25% and 15%. None of the strains were resistant to vancomycin and teicoplanin. Slime production was detected in 86 of 200 CoNS strains. Resistance to methicillin was found in 81% of slime-positive and in 57% of slime-negative strains. Our results indicated that there is a high level of resistance to widely used agents in causative methicillin-resistant CoNS strains. However fusidic acid has the smallest resistance ratio, with the exception of glycopeptides. Additionally, most *S. epidermidis* strains were slime-positive, with

*Corresponding author. Tel.: +90 212 586 1547; fax: +90 212 586 1547.
E-mail addresses: fzkoksal@yahoo.com, , koksal@email.unc.edu (F. Koksal).

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statistically significant ($p<0.001$) association between methicillin resistance and slime production.

Introduction

Coagulase-negative staphylococci (CoNS) found in the normal skin flora and mucous membranes has recently got attention as a potential pathogen, specifically for nosocomial infections (Mandell et al., 2000; Murray et al., 2003; Skov et al., 2003; Mayhall, 2004; Winn et al., 2006). Coagulase-negative bacteremia occurs as a result of long term usage of indwelling central venous catheters, administration of parenteral nutrition and previous antibiotics, patient illness (oncology, burn and high-risk nursery), and other predisposing factors, including intensive-care unit stay, adherence to infection control practices and hand washing practices of medical staff (Mandell et al., 2000; Mayhall, 2004; Winn et al., 2006). There is a significant increase in the methicillin-resistant staphylococci infections and these bacteria have recently started to gain resistance to many widely used antibiotics (Drozenova and Petras, 2000; Livermore, 2000; Mandell et al., 2000; Huang et al., 2003; Murray et al., 2003; Jain et al., 2004; Knauer et al., 2004; Mayhall, 2004; Winn et al., 2006). In spite of the advancements in the antibacterial treatment field, there are still serious difficulties in the treatment of staphylococci infections. In several countries, vancomycin-resistant staphylococci have been isolated (Centers for Disease Control and Prevention, 2002, 2004; Boneca and Chiosis, 2003; Palazzo et al., 2005). One of the most emphasized subjects about pathogenesis of staphylococci infections is the slime production characteristic (Drozenova and Petras, 2000; Huang et al., 2003). Multi-resistant CoNS may adhere to medical devices and surfaces through slime which secretes out of the cell and has a mucopolysaccaride structure, and in this way, they may easily colonize and spread within hospital environment (Mandell et al., 2000; Mayhall, 2004; Winn et al., 2006). Furthermore, the slime factor protects the CoNS from antibiotics, phagocytosis and chemotaxis (Ammendolia et al., 1999; Mandell et al., 2000; Mayhall, 2004).

In this study, we investigated the antibiotic resistance pattern and slime production characteristics of the CoNS-caused nosocomial bacteremia in Istanbul University Cerrahpasa Medical Hospital.

Materials and methods

A total of 200 CoNS strains were isolated from blood samples of patients with true bacteremia who were hospitalized in standard departments and in intensive care units of Istanbul University Cerrahpasa Medical Faculty Hospital between 1999 and 2006. All of these patients had two or more blood cultures positive for CoNS. Among 200 patients, 137 patients were using a central venous catheter or medical device and the others were who have burn and immune deficiency or malignancy. In this study, we used the criteria of true bacteremia (Garner et al., 1988; Herwaldt et al., 1996; Bates et al., 1997). Blood cultures were analyzed with the Bactec 9120 system (Becton Dickinson, France). Positive blood cultures were isolated on Columbia agar base supplemented with 5% horse blood, and the plate was incubated at 35 °C for 24 h. CoNS were detected based on colony morphology, Gram staining and the absence of coagulase activity. The species of CoNS were identified using the API ID 32 Staph (Bio Mérieux, France) and their slime formations were evaluated with Congo red agar method (Freeman et al., 1989).

Antimicrobic susceptibilities of the CoNS strains were determined by the disk diffusion method on Mueller-Hinton agar (bioMérieux, Marcy l'Etoile, France) according to the Clinical and Laboratory Standards Institute (CLSI) (Clinical and Laboratory Standards Institute., 2006). In our study, penicillin, vancomycin, teicoplanin, ciprofloxacin, erythromycin, gentamicin, tetracycline, chloramphenicol, clindamycin, trimethoprim-sulfamethoxazole and fusidic acid (oxoid) disks were used. For fusidic acid, the criteria determined by France Microbiology and Antibiogram Community in 1998 was taken into consideration (Comité de L'antibiogramme de la Société Française de Microbiologie Communiqué, 1998). In this study, the disks containing 10 μg fusidic acid (oxoid) (zone diameter $\geqslant$22 mm sensitive, $<$15 mm resistant) were used for determining the resistance to fusidic acid. The disks containing 1 μg oxacillin (oxoid) (zone diameter $\geqslant$13 mm sensitive, $\leqslant$10 mm resistant) were used for resistance to methicillin (Clinical and Laboratory Standards Institute., 2006). *Staphylococcus aureus* ATCC 25923 and *Staphylococcus epidermidis* ATCC

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35984 were used as quality control organisms. Statistical *p*-value was calculated by Fisher's exact test.

Results

We isolated a total of 200 CoNS strains from blood samples of patients with true bacteremia in intensive care units and in other departments of Istanbul University Cerrahpasa Medical Hospital. The distribution of CoNS according to hospital wards is shown in Table 1. Fourteen different species were identified (87 *Staphylococcus epidermidis*, 23 *Staphylococcus haemolyticus*, 19 *Staphylococcus hominis*, 18 *Staphylococcus lugdunensis*, 15 *Staphylococcus capitis*, 10 *Staphylococcus xylosus*, 8 *Staphylococcus warneri*, 5 *Staphylococcus saprophyticus*, 5 *Staphylococcus lentus*, 4 *Staphylococcus simulans*, 3 *Staphylococcus chromogenes*, 1 *Staphylococcus cohnii*, 1 *Staphylococcus schleiferi*, and 1 *Staphylococcus auricularis*).

Methicillin resistance in CoNS was determined to be 67.5%. The antimicrobial resistance patterns of the strains are shown in Table 2. The resistance ratios to ciprofloxacin, erythromycin, gentamicin, tetracycline, clindamycin and trimethoprim-sulfamethoxazole were found to be extremely high in the methicillin-resistant strains compared to those that were susceptible to methicillin ($p<0.001$). The lowest resistance ratio in the methicillin-resistant staphylococci was detected for fusidic acid (25%). There was no resistance to vancomycin and teicoplanin.

Slime positivity was 43% in CoNS strains; 52% of which was in MR-CoNS, and 25% in MS-CoNS. Methicillin resistance was found to be significantly higher in slime positive strains (81%) t han in slime negative strains (57%) ($p<0.001$) (Table 3).

The slime positivity was higher (71%) in *S. epidermidis* than the other staphylococcus species (35% in *S. haemolyticus*, 26% in *S. hominis*, 22% in *S. lugdunensis*, 10% in *S. xylosus*, 7% in *S. capitis*) ($p = 0.002$). The slime production was determined in only one of *S. saprophyticus*, *S. simulans*, and *S. schleiferi* isolates (Table 4).

Table 1. The distribution of CoNS according to hospital wards

Hospital ward	CoNS
Intensive care	60
Child surgery	35
Emergency burn care	29
Neurosurgery	24
Internal medicine	23
Newborn intensive care	10
Oncology	5
Neurology	3
Haematology	3
Ortopedy	3
Obstetrics and Gynecology	3
Urology	2
Total	200

Table 3. The distribution of slime-producing according to methicilline resistance

CoNS ($N = 200$)	Slime positive $n = 86$ (43%)	Slime negative $n = 114$ (57%)
MR $n = 135$ (67.5%)	70 (52)	65 (48)
MS $n = 65$ (32.5%)	16 (25)	49 (75)

Table 2. The antibiotic resistance ratios of the strains that are resistant (MR) and susceptible to methicilin (MS)(%)

$N = 200$	MR-CoNS $n = 135$ (67.5%)	MS-CoNS $n = 65$ (32.5%)	*p*-value
Vancomycin 30 μg	0	0	
Teicoplanin 30 μg	0	0	
Fusidic acid 10 μg	25	15	0.117
Chloramphenicol 30 μg	56	13	<0.001
Tetracycline 30 μg	60	45	0.058
Ciprofloxacin 5 μg	67	23	<0.001
Trimethoprim/sulfamethoxazole 1.25/23.75 μg	68	38	<0.001
Clindamycin 2 μg	72	18	<0.001
Erythromycin 15 μg	80	37	<0.001
Gentamicin 10 μg	90	17	<0.001
Penicillin 10 units	—	91	

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Table 4. The distribution of 200 CoNS strains according to species and their slime production

CoNS	*n* (%)	Slime positive *n* (%)
S. epidermidis	87 (43.5)	62 (71)
S. haemolyticus	23 (11.5)	8 (35)
S. hominis	19 (9.5)	5 (26)
S. lugdunensis	18 (9.0)	4 (22)
S. capitis	15 (7.5)	1 (7)
S. xylosus	10 (5.0)	1 (10)
S. warneri	8	0
S. saprophyticus	5	1
S. lentus	5	0
S. simulans	4	1
S. chromogenes	3	0
S. auricularis	1	0
S. cohnii	1	0
S. schleiferi	1	1

Discussion

CoNS are a major cause of nosocomial bacteremia and septicemia, especially for the patients who have immune deficiency and malignancy, which can lead to morbidity and even mortality (Mayhall, 2004). Despite the recent introduction of antimicrobial agents and medical improvements in controlling the frequency and morbidity of staphylococci infections, they are persistent as an important hospital and community pathogen. Furthermore, these bacteria have become a major concern to the medical community due to the fact that they have an extraordinary ability to adapt rapidly to antibiotic stress (Livermore, 2000). Because of the widespread use of penicillin in 1950s, penicillin-resistant Staphylococci spread in hospitals. Afterwards methicillin and its derivatives became the drugs of choice for the treatment of infections caused by staphylococci. Soon thereafter, methicillin-resistant staphylococci were reported (Mayhall, 2004). All methicillin-resistant CoNS have been displayed to contain a mecA gene or its gene product, PBP-2a, and it may easily spread to all methicillin-resistant CoNS, probably through transposons (Mayhall, 2004). Methicillin-resistant staphylococci are resistant to all other penicillins, carbapenems, cephems and beta-lactam/beta-lactamase inhibitor combinations (Clinical and Laboratory Standards Institute., 2006). Consequently, these antibiotics should not be used for treating of methicillin-resistant staphylococci infections (Clinical and Laboratory Standards Institute., 2006). Recently, several studies have shown that the methicillin-resistant staphylococci have started to gain resistance to many widely used antibiotics (quinolone, macrolide group antibiotics, aminoglycosides, tetracycline, trimethoprim-sulphamethoxazole, clindamycin, chloramphenicol) (Drozenova and Petras, 2000; Huang et al., 2003; Jain et al., 2004; Knauer et al., 2004).

In our study, the resistance to methicillin was determined in 67.5% of CoNS isolates. A comparison of our results with data from previous study done in the same hospital showed that the methicillin resistance has increased rapidly (from 38% to 67.5%) (Koksal et al., 1996). The ratios of resistance to other antibiotics in methicillin-resistant CoNS were found to be quite high for gentamicin (90%), erythromycin (80%), clindamycin (72%), trimethoprim-sulphamethoxazole (68%), ciprofloxacin (67%), tetracycline (60%) and chloramphenicol (56%) ($p<0.001$).

Other studies have reported 54–92% resistance ratios to gentamicin that has been used along with a beta-lactamase-stable penicillin for ampirical treatment of sepsis since early 1970s (Drozenova and Petras, 2000; Ertek et al., 2002; Huang et al., 2003; Skov et al., 2003; Klingenberg et al., 2004). The transfer of gentamicin resistance determinants usually residing on conjugative plasmids has been shown between species of coagulase-negative staphylococci and between *S. epidermidis* and *S. aureus* (Mayhall, 2004). Furthermore in many studies, high resistance ratios against erythromycin, clindamycin, tetracycline and ciprofloxacin were reported (Gristina et al., 1989; Drozenova and Petras, 2000; Ertek et al., 2002; Huang et al., 2003). Additionally, prolonged therapy with quinolones may lead to the development of cross-resistance in methicillin-resistant staphylococci (Clinical and Laboratory Standards Institute., 2006). In various reports, the resistance to chloramphenicol was found to be 48–68% (Drozenova and Petras, 2000; Knauer et al., 2004; Palazzo et al., 2005). The resistance increase against trimethoprim-sulfamethoxazole, which is an alternative medicine in the treatment of methicillin-resistant staphylococci infections is recently receiving attention. Previously, trimethoprim-sulfamethoxazole resistance has been shown to be 10–53% in Turkey, while it was reportedly higher (47–76%) in European countries (Gristina et al., 1989; Koksal et al., 1996; Mandell et al., 2000; Asrat and Amanuel, 2001; Altoparlak et al., 2004; Mayhall, 2004; Sakarya et al., 2004). The resistance ratio that we found for this agent showed that this difference is getting smaller.

Our results indicated that resistance ratio in the methicillin-resistant staphylococci is 25% for fusidic acid which is considerably lower than other agents. Similar results were also found in other studies that were done in Turkey and elsewhere (Coutant et al.,

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1996; Asrat and Amanuel, 2001; Skov et al., 2003; Altoparlak et al., 2004; Jain et al., 2004). Fusidic acid is an important second-line agent used for the treatment of multi-resistant staphylococci infections (Hiramatsu et al., 1997; Skov et al., 2003).

None of our CoNS strains were resistant to vancomycin and teicoplanin. However in the United States and Japan, it has been reported that the susceptibility to glycopeptides was reduced (Jones et al., 1998; Boisson et al., 2002). Vancomycin has long been considered as an antibiotic of last resort for multi-drug-resistant staphylococci infections (Ludwicka et al., 1984; Mayhall, 2004). On the other hand, vancomycin resistance has emerged first in enterococci and, more recently, in *S. aureus* and coagulase-negative staphylococci (Centers for Disease Control and Prevention, 2002, 2004; Boneca and Chiosis, 2003; Palazzo et al., 2005). This condition has led CoNS to become a serious health problem that medical practitioners should be concerned about. The extensive use of glycopeptides in hospitals has been related to decreased susceptibility to these agents. Unfortunately, the therapy chance of multi-resistant staphylococci infections is gradually decreasing.

Among 200 CoNS isolated in our hospital, *S. epidermidis* was the most prevalent species. The slime positivity was 71% in this species ($p<0.001$). We determined slime production in 35% of *S. haemolyticus*, in 26% of *S. hominis*, in 22% of *S. lugdunensis*, in 10% of *S. xylosus*, in 7% of S. capitis. Similar percentages of slime-positive *S. epidermidis* and other species were also reported in different studies (Davenport et al., 1986; Diaz-Mitoma et al., 1987; Deighton et al., 1988; Christensen et al., 1992; Udo et al., 1995; Ammendolia et al., 1999; Ertek et al., 2002; Bartoszewicz et al., 2003). The slime production was observed in only one of *S. saprophyticus*, *S. simulans*, and *S. schleiferi* isolates. Slime production was reported in 50% of *S. saprophyticus* by Deighton et al. (1988). To our knowledge there is no study about slime production of *S. schleiferi*. It has been reported that the slime production is higher in the pathogenic CoNS strains rather than CoNS in normal flora (Davenport et al., 1986; Diaz-Mitoma et al., 1987; Christensen et al., 1992; Drozenova and Petras, 2000). The slime production by CoNS is accepted by some to be associated with pathogenicity, but the relationship between slime production and antibiotic resistance is a matter of debate (Davenport et al., 1986; Diaz-Mitoma et al., 1987; Christensen et al., 1992; Oto et al., 1998; Ertek et al., 2002; Bartoszewicz et al., 2003; Sakarya et al., 2004; Malm et al., 2005). This study showed that methicillin resistance was higher in slime producing strains (81%) than in non-slime producing strains (57%) ($p<0.001$).

CoNS may adhere to medical devices and surfaces through slime, and the slime allows multi-resistant CoNS to colonize within hospital environment. Thus, they may serve as a reservoir of antimicrobial resistance determinants in hospital. It seems that the therapy of multi-resistant staphylococci infections could become difficult in the near future. For this reason, it is necessary to take preventive measures in order to limit the colonization and spread of multi-resistant staphylococci within hospital environment before a nosocomial infection with these organisms starts.

In conclusion, methicillin-resistant CoNS isolated from blood cultures of patients with true bacteremia show that there is a high level of resistance to commonly used agents, with fusidic acid displaying the least resistance ratio. Most of strains of *S. epidermidis* have the slime positivity, and the association between methicillin-resistant and slime production was statistically significant. This study shows that it is important to monitor antibiotic consumption and resistance trends of nosocomoal staphylococci, especially with infection control measures to prevent emergence and spread of multi-resistant bacteria within the hospital environment.

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