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Clinical significance and staphylococcal cassette chromosome mec (SCC*mec*) characterization of coagulase-negative staphylococci isolated from blood cultures

Gürkan MERT[1], Abdullah KILIÇ[2], Orhan BEDİR[2], Ahmet Celal BAŞUSTAOĞLU[2]

Aim: To describe the true coagulase-negative staphylococci (CoNS) bacteremia rate compared with contaminants, and to determine the *SCCmec* types in methicillin-resistant staphylococci and evaluate the diversity between methicillin-resistant CoNS (MRCoNS) and methicillin-resistant Staphylococcus aureus (MRSA) isolates during a 10-month study period.

Materials and methods: The true CoNS bacteremia or bloodstream infection episode was defined on the basis of previous studies on CoNS bacteremia and the definitions of the Centers for Disease Control and Prevention. *SCCmec* types were determined by using the real-time PCR method. A total of 357 staphylococci isolates, including 313 CoNS and 44 *S. aureus*, were obtained from 462 positive blood culture samples.

Results: A total of 249 CoNS bacteremia episodes in 231 patients were evaluated. Of these episodes, 45 (18.1%) in 41 patients were considered to be true CoNS bacteremia, whereas 204 in 190 patients were found to be contaminant. In the present study, all of the MRSA isolates harbored only SCC*mec* type III, but MRCoNS strains harbored different SCC*mec* types and *SCCmec* type IV was the most prevalent.

Conclusion: The true CoNS bacteremia rate was consistently within the range reported in the literature. We also concluded that MRCoNS isolates carrying mostly *SCCmec* type IV elements may not be related to the presence of MRSA isolates carrying only *SCCmec* type III element in our institution.

Key words: *SCCmec* types, CoNS, TaqMan real-time PCR, Turkey

Kan kültürlerinden izole edilen koagulaz negatif stafilokokların klinik önemi ve stafilokokal kaset kromozom (SCC*mec*) özellikleri

Amaç: Çalışmanın birinci amacı gerçek KNS bakteriyemi oranını kontaminasyon ile karşılaştırarak tanımlamaktır. İkinci amaç ise on aylık çalışma süresince, metisiline dirençli KNS (MRKNS) ve metisiline dirençli *Staphylococcus aureus* (MRSA) izolatları arasındaki farklılıkları değerlendirmek ve metisiline dirençli stafilokoklarda *SCCmec* tiplerini belirlemektir.

Yöntem ve gereç: Gerçek KNS bakteriyemi ya da kan dolaşımı enfeksiyonları CDC tarafından önceki çalışmalarda tarif edilmiş ve belirlenmiştir. Çalışmada, *SCCmec* tipleri real-time PCR yöntemi kullanılarak belirlenmiştir. Toplam 462 pozitif kan kültürü örneğinden 357 stafilokok (313'ü KNS ve 44'ü *S. aureus*) izole edildi.

Bulgular: 231 hastada oluşan 249 KNS bakteriyemi epizotu değerlendirildi. KNS bakteriyemi epizotu tanımlanmış olan 41 hastanın 45 epizotu (% 18,1) gerçek KNS bakteriyemisi olarak düşünülürken, 190 hastada tanımlanan 204 epizot kontaminasyon olarak değerlendirildi. Çalışmada, tüm MRSA suşları sadece *SCCmec* III tipini barındırmasına karşın MRKNSlar farklı *SCCmec* tipleri ve özellikle tip IV'ü en yaygın olarak barındırmaktaydı.

Sonuç: Çalışmada gerçek KNS bakteriyemi oranları literatür ile uyumludur. Kurumumuzda, çoğunlukla *SCCmec* tip IV taşıyan MRKNS izolatlarının sadece *SCCmec* tip III taşıyan MRSA izolatları ile ilişkili olmadığı sonucuna varılmıştır.

Anahtar sözcükler: *SCCmec* tipleri, KNS, TaqMan real-time PCR, Türkiye

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[1] Department of Infectious Diseases, Gülhane Military Medical Academy and Faculty of Medicine, 06018 Etlik, Ankara - TURKEY
[2] Department of Microbiology and Clinical Microbiology, Gülhane Military Medical Academy and Faculty of Medicine, 06018 Etlik, Ankara - TURKEY
Correspondence: *Gürkan MERT, Department of Infectious Diseases and Clinical Microbiology, Gülhane Military Medical Academy, Faculty of Medicine, 06018 Ankara - TURKEY*
E-mail: gmert@gata.edu.tr

Introduction

Staphylococcus species are the most important cause of life-threatening bloodstream infections in the United States and in some European countries (1). Coagulase-negative staphylococci (CoNS) have been reported worldwide and are an important pathogen causing nosocomial bacteremia (2,3). These organisms are also known as the most common blood culture contaminant, since they are the most common microorganisms found colonizing the skin and mucous membranes. Therefore, it is difficult to determine which CoNS isolates recovered from blood cultures represent true infection and which are contaminants (4). However, identification of true CoNS bacteremia is extremely important to avoid inappropriate use of glycopeptide agents (5).

Methicillin resistance in the *Staphylococcus* species is mediated by the production of a low-affinity penicillin-binding protein (PBP2a) that is encoded by the *mecA* gene, located on a large mobile genetic element, the staphylococcal chromosomal cassette *mec* (SCC*mec*) (6). SCC*mec* elements have been identified in 6 different allotypes in *S. aureus* and 5 different allotypes in CoNS isolates, according to the combination of the *mec* gene complex class and the *ccr* gene complex type (7,8). The large groups of MRCoNS isolates carrying SCC*mec* elements are a possible reservoir and donor of resistance genes that can possibly be transferred to other gram-positive organisms such as *S. aureus*. However, the possible mechanisms for the horizontal transfer of SCC*mec* elements from CoNS to *S. aureus* are not known (9).

The first aim of this study was to describe the true CoNS bacteremia rate compared with contaminants. The second aim was to determine the SCC*mec* types and to evaluate the diversity between MRCoNS and MRSA isolates at the Gülhane Military Medical Academy Hospital (GMMAH) during a 10-month study period. To our knowledge, this is the first report from Turkey based on molecular SCC*mec* typing analysis of MRCoNS isolates collected from a hospital setting.

Materials and methods

Definition of CoNS bacteremia and contaminant

A true CoNS bacteremia or bloodstream infection episode was defined on the basis of previous studies of CoNS bacteremia (10-13) and the definitions of the Centers for Disease Control and Prevention (CDC) (14). In brief, CoNS bacteremia was declared if the same CoNS isolate was isolated from at least 2 sets of blood cultures at separate time intervals within a 5-day period, combined with at least 1 of the following signs or symptoms: fever (>38 °C), hypothermia (<37 °C), and apnea, or bradycardia.

Bacterial isolates

GMMAH is a teaching hospital with more than 1500 beds in Ankara, the capital of Turkey. Approximately 6000 blood culture bottles are processed in the microbiology laboratory in a year. Patients' whole blood was inoculated into BACTEC blood culture bottles (Becton Dickinson Diagnostic Instrument Systems, Sparks, MD, USA) and incubated in the BACTEC 9240 system (Becton Dickinson Diagnostic Instrument Systems). When a positive signal was indicated, a portion of the blood culture medium was inoculated onto 5% sheep blood agar (Difco, Sparks, MD, USA) and chocolate agar (Difco) plates for subculture and further identification. Plates were incubated at 35 °C aerobically in a 5% CO_2 environment for 24-48 h. Bacterial isolates were identified initially by colony morphology, Gram staining, catalase, and tube coagulase tests, and identified further by the BD Phoenix Automated Microbiology System (Becton Dickinson Diagnostic Systems) (15). To avoid overrepresentation, only the first isolate from each patient during the study period was included. The isolates were stored at –70 °C in trypticase soy broth (Merck, Darmstadt, Germany) supplemented with 15% glycerol before being tested.

Antimicrobial susceptibility testing

The susceptibility of the isolates was determined against 13 antimicrobial agents by a disk diffusion method in accordance with Clinical and Laboratory Standards Institute standards (CLSI) (16). The penicillin-binding protein 2' latex agglutination test (PBP2') (Oxoid Limited, Basingstoke, England) was also performed for the confirmation of the *mecA*-positive staphylococci species as recommended by

the manufacturers. *S. aureus* ATCC 29213 and MRSA NCTC 10442 were used as control strains.

SCC*mec* typing

DNA was prepared as described previously by Kilic et al. (17). A real-time TaqMan PCR was performed on the ABI Prism 7500 sequence detector (Applied Biosystems, Foster City, CA, USA). The primers and fluorophore TaqMan probes for SCC*mec* types I, II, III, IV, and V were used as described previously (15). The TaqMan cycling conditions were a 2-min degradation of the preamplified templates at 50 °C, then 40 cycles of denaturation at 95 °C for 15 s and annealing and extension at 58 °C for 60 s.

Statistical analysis

Statistical comparisons were performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Associations between the true CoNS bacteremia and the contaminant for isolated organisms and antibiotic resistance were analyzed using the chi-square test or Student's t-test. $P \leq 0.05$ was considered statistically significant.

Results

During a 10-month period from November 2008 to August 2009, 4323 blood culture samples were processed at GMMAH. In the 462 positive blood culture samples collected during that period, a total of 357 staphylococci isolates, including 313 CoNS and 44 *S. aureus*, were obtained. Isolates were identified by using the conventional methods described above as 261 MRCoNS, 52 methicillin-susceptible coagulase-negative staphylococci (MSCoNS), 22 MRSA, and 22 methicillin-susceptible *S. aureus* (MSSA) (Table 1).

A total of 249 CoNS bacteremia episodes in 231 patients were evaluated. Of these episodes, 45 (18.1%) in 41 patients were considered to be true CoNS bacteremia, whereas 204 in 190 patients were found to be contaminant. *S. epidermidis* was the most common isolate in both true CoNS bacteremia (50 of 90 isolates [55.5%]) and contamination (92 of 223 isolates [41.2%]), and it had a statistically higher rate in true CoNS bacteremia ($P = 0.021$) (Table 1). Methicillin resistance was found to be

Table 1. CoNS strains isolated from blood culture samples considered to be true CoNS bacteremia and contaminants.

Species	No. (%) of isolates			
	Total n = 313	True CoNS bacteremia; total n = 90	Contaminants; total n = 223	P-value
S. epidermidis	142 (45.3)	50 (55.5)	92 (41.2)	0.021
S. hominis	96 (30.6)	20 (22.2)	76 (34.1)	0.039
S. haemolyticus	32 (10.2)	14 (15.5)	18 (8.1)	0.047
S. capitis	13 (4.1)	-	13 (5.8)	0.020
S. saprophyticus	12 (3.8)	2 (2.2)	10 (4.4)	0.345
S. warneri	9 (2.8)	2 (2.2)	7 (3.1)	0.660
S. xylosus	4 (1.2)	2 (2.2)	2 (0.8)	0.344
S. lugdunensis	1 (0.3)	-	1 (0.4)	0.524
S. cohnii	1 (0.3)	-	1 (0.4)	0.524
S. equorum	1 (0.3)	-	1 (0.4)	0.524
S. chromogenes	1 (0.3)	-	1 (0.4)	0.524
S. hyicus	1 (0.3)	-	1 (0.4)	0.524

83.3% (261/313) among CoNS isolates (Table 2). Methicillin resistance was more frequently detected among *S. epidermidis* isolates in both the true CoNS bacteremia (96%) and the contaminants (82.6%) (Table 3).

We tested 22 MRSA and 261 MRCoNS isolates for SCC*mec* types using the TaqMan real-time method. SCC*mec* type III was detected in all MRSA isolates. In 261 MRCoNS isolates, SCC*mec* types I, II, III, IV, V, and some combinations of these types were detected in 61 (23.3%), 0 (0%), 31 (11.8%), 65 (24.9%), 37 (14.1%), and 46 (17.6%) isolates, respectively (Table 4).

Discussion

Suggested laboratory criteria for true CoNS bacteremia include multiple blood cultures positive for the same organisms and growth within a 5-day period. True CoNS bacteremia and contaminant rates have been reported in bacteremic patients all over the world. Finkelstein et al. (13) reported that the true CoNS bacteremia rate was 30% in a total of 137 episodes occurring among 122 patients. Beekmann et al. (18) screened a total of 960 consecutive patients with positive blood cultures and reported a significant bacteremia rate of 22%. Souvenir et al. (11) reported that the true CoNS bacteremia rate was 24.7% in a total of 3276 blood cultures from 1433 patients. In our study, the true CoNS bacteremia rate in 249 episodes was 18.1%, consistent with the 6%-30% range reported in the literature (3,10,11,13,18-20).

S. epidermidis, *S. haemolyticus*, and *S. hominis* are the most frequently recovered CoNS isolates in blood cultures (21-24). Mombach Pinheiro Machado et al. (22) indicated that *S. epidermidis* was the most common species (67.4%), followed by *S. haemolyticus* (11.6%) and *S. hominis* (10.1%), in bacteremia patients at a tertiary hospital in

Table 2. Antibiotic resistance profiles of CoNS strains isolated from blood culture samples.

Antibiotics	No. (%) of resistant			
	Total n = 313	True CoNS bacteremia; total n = 90	Contaminants; total n = 223	P-value
Methicillin	261 (83.3)	82 (91.1)	179 (80.2)	0.013
Amoxicillin-clavulanate	256 (81.7)	79 (87.7)	177 (79.3)	0.081
Cefazolin	255 (81.4)	79 (87.7)	176 (78.9)	0.061
Clindamycin	104 (33.2)	30 (33.3)	74 (33.1)	0.970
Erythromycin	247 (78.9)	73 (81.1)	174 (78.1)	0.544
Levofloxacin	204 (65.1)	68 (75.5)	136 (60.9)	0.014
Moxifloxacin	112 (35.7)	35 (38.8)	77 (34.5)	0.466
Penicillin	285 (91.1)	81 (90)	204 (91.4)	0.677
Rifampin	175 (55.9)	46 (51.1)	129 (57.8)	0.277
Mupirocin	164 (52.3)	43 (47.7)	121 (54.2)	0.298
Trimethoprim/sulfamethoxazole (SXT)	177 (56.5)	52 (58)	125 (56.1)	0.780
Vancomycin	-	-	-	-
Linezolid	-	-	-	-
Inducible clindamycin resistance	100 (31.9)	30 (33.3)	70 (31.3)	0.891

Table 3. The most common CoNS strains isolated from blood culture samples considered to be true CoNS bacteremia and contaminants.

Species	No. (%) of methicillin resistance			
	Total n = 231	True CoNS bacteremia; total n = 78	Contaminants; total n = 151	P-value
S. epidermidis (n = 142)	124 (87.3)	48 (96)	76 (82.6)	0.021
S. hominis (n = 96)	79 (82.2)	18 (90)	61 (80.2)	0.310
S. haemolyticus (n = 32)	28 (81.2)	12 (85.7)	14 (77.7)	0.568

Table 4. Distribution of SCC*mec* types of MRSA and MRCoNS strains isolated from blood culture samples.

SCC*mec* types	No. (%) of SCC*mec* type resistances		
	MRSA strains; total n = 22	True MRCoNS strains; total n = 82	Contaminant MRCoNS strains; total n = 179
SCC*mec* type I	-	15 (58.5)	46 (25.6)
SCC*mec* type II	-	-	-
SCC*mec* type III	22 (100)	9 (10.9)	22 (12.2)
SCC*mec* type IV	-	22 (26.8)	43 (24.1)
SCC*mec* type V	-	13 (15.8)	24 (13.4)
Mix SCC*mec* type	-	13 (15.8)*	33 (18.4)**
Nontypeable	-	10 (12.1)	11 (6.1)

*SCC*mec* types I-V (n = 3), II-V (n = 6), and II-V (n = 4).
**SCC*mec* I-III (n = 2), I-IV (n = 4), I-V (n = 9), II-V (n = 9), and III-V (n = 3).

southern Brazil. Gaterman et al. (23) reported from Germany that *S. epidermidis*, *S. haemolyticus*, and *S. hominis* were present at 67.4%, 11.9%, and 7.5% in blood culture samples, respectively. Koksal et al. (25) from Turkey indicated that *S. epidermidis* was the most prevalent species (43.5%), followed by *S. haemolyticus* (11.5%) and *S. hominis* (9.5%), among 200 true CoNS bacteremia isolates. In the present study, *S. epidermidis* was the most common isolate, consistent with previous studies in both true CoNS bacteremia (55.5%) and contaminants (41.2%), and it had a statistically higher rate in true CoNS bacteremia (P = 0.021).

Like MRSA, isolation rates of MRCoNS isolates have been increasing rapidly worldwide and have become an important cause of nosocomial infections since the introduction of methicillin. Piette et al. (21) screened different studies and reported MRCoNS rates in clinical samples at between 55% and 77%. These rates have even been reported as high as 86% in intensive care units. In Turkey, these rates were found to vary from 67.5% to 85% (25-27). In the present study, overall methicillin resistance was determined at 83.3% in the 313 CoNS isolates, consistent with the rates of other studies in the literature. Methicillin resistance was found to be

statistically higher in true CoNS bacteremia (82/90, 91.1%) than in contaminants (179/223, 80.2%) (P = 0.013). CoNS isolates recovered from true CoNS bacteremia were also more resistant to amoxicillin-clavulanate (P = 0.081), cefazolin (P = 0.061), and levofloxacin (P = 0.014) than those recovered from contaminants.

The SCC*mec* element is a mobile genetic element widely distributed among CoNS species and *S. aureus*. Varied SCC*mec* types in MRCoNS have been distributed and are dominant in different countries. SCC*mec* type III has been found to be the most prevalent in southern Brazil (52%) (22), whereas SCC*mec* type IV has been reported to be the most common in the United Kingdom (36%) (9) and Finland (33%) (7). In China, SCC*mec* type II has been observed as the most common type (28). In the present study, SCC*mec* type IV MRSA isolate was the most common (24.9%) among all of the MRCoNS isolates. This result was consistent with previous studies reported from European countries.

Horizontal transfer of SCC*mec* elements in CoNS might contribute to the dissemination of MRSA throughout the world, since CoNS are known to carry SCC*mec* elements at a high frequency as a possible reservoir of resistance genes. The horizontal transfer of *mecA* DNA from CoNS to *S. aureus* was observed in a previous study (29). The hypothesis of SCC*mec* transfer between *S. epidermidis* and *S. aureus* has also been reported in the literature (7,30). In the present study, all of the MRSA isolates harbored only SCC*mec* type III, but MRCoNS isolates harbored different SCC*mec* types and SCC*mec* type IV was the most prevalent. We concluded that MRCoNS isolates carrying mostly SCC*mec* type IV elements may not be related to the presence of MRSA isolates carrying only SCC*mec* type III element in our institution.

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