First report of methicillin-resistant Staphylococcus aureus carrying the mecC gene in human samples from Iran: prevalence and molecular characteristics

M. Goudarzi1,2, M. Navidinia3, M. Dadashi5, A. Hashemi1 and R. Pouriran4

1) Infectious Diseases and Tropical Medicine Research Center, 2) Department of Microbiology, School of Medicine, 3) School of Allied Medical Sciences, 4) School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran and 5) Department of Microbiology, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran

Abstract

There is a lack of information concerning mecC clinical methicillin-resistant Staphylococcus aureus (MRSA) strains throughout the world. In the present survey, 345 MRSA strains were characterized by antimicrobial susceptibility testing and staphylococcal cassette chromosome mec (SCCmec) typing. mecC-positive MRSA isolates were characterized by study of biofilm formability, adhesion and virulence analysis, multilocus sequence typing, accessory gene regulator (agr) typing, S. aureus protein A locus (spa) typing and staphylocoagulase typing. The present study found ten SCCmec types, with the majority being SCCmec type III (38.3%). The presence of mecC was confirmed in three isolates from skin wounds (two isolates) and burn wounds (one isolate). All the mecC-positive isolates carried SCCmec XI and belonged to coa type III. Molecular typing showed that these isolates belonged to clonal complex/ST130-spa type t843-agr type III (two isolates) and clonal complex/ST599-spa type 5930-agr type I. The presence of SCCmec type IV confirms the hypothesis of extensive infiltration from the community to the hospital. Detection of MRSA isolates harbouring the mecC gene highlights the need to perform routine detection methods and molecular investigations in order to identify these emerging strains and limit their transfer in hospitals and communities.

Keywords: Agr allotype, mecC, MLST, MRSA, PCR, spa, Staphylococcus aureus

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Corresponding author: M. Goudarzi, Department of Microbiology, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Koochak-yar St, Daneshjoo Blvd, Velenjak, Chamran Hwy, Tehran, Iran. E-mail: goudarzim@yahoo.com

Introduction

Methicillin-resistant Staphylococcus aureus (MRSA) is an opportunistic pathogen responsible for many nosocomial infections [1,2]. Over the past few decades, the emergence of MRSA strains in the community and infection in patients without previous healthcare contact has become a matter of concern worldwide [1,2]. Resistance to methicillin is mediated by the mecA gene, which encodes an altered penicillin-binding protein (PBP2a/PBP2') and is carried on the staphylococcal cassette chromosome mec element (SCCmec) [3]. SCCmec is composed of two essential genetic components (the ccr gene complex (ccr) and the mec gene complex) and the junkyard (J) regions. The ccr gene complex consists of ccr genes and surrounding open reading frames, which mediate the mobility of SCCmec. The mec gene complex is composed of the mecA gene, regulatory genes of mecR1-mecI and different insertion sequences. Several types of SCCmec elements have been described on the basis of the combinations of mec and ccr complexes. Recently, mecC, a mecA homolog provisionally named mecA5, was reported in a small number of animal sources [4]. The mecC is located in a new SCCmec cassette type XI and exhibits 69% homology with mecA and 63% identity to the PBP2a encoded by mecA [5].
Limited data are available on MRSA isolates carrying the mecC gene in Iran. Hence, the present research investigated the distribution of different SCCmec types and the prevalence of mecC-positive MRSA isolates. Multilocus sequencing typing (MLST), accessory gene regulator (agr) typing, S. aureus protein A locus (spa) typing and staphylococcalase typing were used to characterize the genotype of the mecC-positive MRSA isolates.

Materials and methods

Bacterial isolates
In the present study, 345 MRSA strains were randomly selected from stored isolates collected from different clinical microbiology laboratories between 2015 and 2019 in Tehran, Iran. The sources for the isolation of the strains included skin wounds (27.8%), purulent exudates (18.8%), burn wounds (13.4%), urine (11.3%), blood (10.4%), surgical wounds (10.1%), respiratory tract secretions (5.8%) and other body fluids (1.5%). Ethical approval for this study was obtained from the ethics committee of Shahid Beheshti University of Medical Sciences in Tehran, Iran (IR.SBMU.MSP.REC.1398.816). All strains were isolated and identified using standard bacteriologic techniques and PCR analysis of fem and nuc genes [6]. MRSA strains were identified by the disc diffusion method using cefoxitin (30 μg) discs on Muller-Hinton agar (Merck, Germany) using the 2019 Clinical and Laboratory Standards Institute (CLSI) guidelines and detection of the mecA gene as previously described [6].

Evaluation of antimicrobial activities
Antibiotic susceptibility was performed by the Kirby-Bauer disc diffusion method against kanamycin (KAN), gentamicin (GEN), tobramycin (TOB), amikacin (AMK), clindamycin (CLI), quinupristin/dalfopristin (SYN), tetracycline (TET), erythromycin (ERY), rifampin (RIF), teicoplanin (TEC), linezolid (LIN), ciprofloxacin (CIP) and trimethoprim/sulfamethoxazole (SXT) (Mast, UK) and interpreted according to the 2019 CLSI guidelines. MIC values for the antibiotics vancomycin and erythromycin (ERY), rifampin (RIF), teicoplanin (TEC), linezolid (LIN), ciprofloxacin (CIP) and trimethoprim/sulfamethoxazole (SXT) were determined using the broth microdilution guidelines. MIC values for the antibiotics vancomycin and tobramycin (TOB), amikacin (AMK), clindamycin (CLI), quinupristin/dalfopristin (SYN), tetracycline (TET), erythromycin (ERY), rifampin (RIF), teicoplanin (TEC), linezolid (LIN), ciprofloxacin (CIP) and trimethoprim/sulfamethoxazole (SXT) were determined using the broth microdilution guidelines. MIC values for the antibiotics vancomycin and erythromycin (ERY), rifampin (RIF), teicoplanin (TEC), linezolid (LIN), ciprofloxacin (CIP) and trimethoprim/sulfamethoxazole (SXT) were determined using the broth microdilution guidelines. MIC values for the antibiotics vancomycin and tobramycin (TOB), amikacin (AMK), clindamycin (CLI), quinupristin/dalfopristin (SYN), tetracycline (TET), erythromycin (ERY), rifampin (RIF), teicoplanin (TEC), linezolid (LIN), ciprofloxacin (CIP) and trimethoprim/sulfamethoxazole (SXT) were determined using the broth microdilution guidelines. MIC values for the antibiotics vancomycin and tobramycin (TOB), amikacin (AMK), clindamycin (CLI), quinupristin/dalfopristin (SYN), tetracycline (TET), erythromycin (ERY), rifampin (RIF), teicoplanin (TEC), linezolid (LIN), ciprofloxacin (CIP) and trimethoprim/sulfamethoxazole (SXT) were determined using the broth microdilution guidelines.

mecC gene detection
All MRSA isolates were subjected to PCR assay for the presence of the mecC gene with forward (5′-GAA AAA AAG GCT TAG AAC GCCTC-3′) and reverse (5′-GAA GAT CTT TTC CGT TTT CAG C-3′) primers as previously described by Garcia-Álvarez et al. [7]. Positive PCR products were sequenced to confirm the identification of the mecC gene. MRSA isolates harbouring mecC were subjected to PCR targeting S. aureus mec complex E and ccr complex B to confirm the presence of SCCmec type XI [8].

Phenotypic analysis of biofilm formation
The MRSA isolates carrying the mecC gene were investigated for biofilm formation using in vitro microtitre plate assay according to the procedure described by Yousefi et al. [9]. The Staphylococcus epidermidis ATCC 35984 strain was used as the control positive strain for biofilm formation.

DNA isolation and screening for resistance, virulence and biofilm-related genes
Genomic DNA extraction was carried out using the phenol–chloroform method as described previously [10]. All isolates were screened for resistance encoding genes, namely: vanA, vanB, mupB, mupA, fusA, fusB, fusC, msr(A), msr(B), erm(A), erm(B), erm(C), tetM, tetL, tetQ, tetK, ant (4′)-Ia, aac (6′)-Ie-aph (2′) and aph (3′)-IIa and virulence encoding genes including exfoliative toxin genes (eta and etb), Panton-Valentine leukotoxin (pvA) and toxic shock toxin (tst) genes by PCR assay with oligonucleotide primers as previously described. PCR assay was also used to evaluate biofilm by the presence of icaABCD, can, ebp, fnbA, fnbB and bap genes [10].

Molecular typing methods
The MRSA isolates were subjected to multiplex PCR to type and subtype the SCCmec elements using the specific primers and protocol described by Ghaznavi-Rad et al. [11]. The MRSA isolates carrying the mecC gene underwent spa typing by amplification of the polymorphic X region of the spa gene by PCR with forward (5′-AGACGATCCTCGGAGC-3′) and reverse (5′-GCTTGGCAATGCTATTTACTG-3′) primers as recommended by Harmesen et al. [12]. The agr types of mecC-positive isolates were determined by multiplex PCR assay as described by Gilot et al. [13]. Coagulase typing was also performed by multiplex PCR assay according to the procedure of Hirose et al. [14]. The mecC positive isolates were further characterized by MLST by amplifying and sequencing seven housekeeping genes (pta, arcC, tpi, aroE, gmk, yqiL, gip). Sequence types (STs) were determined by submitting the allelic profile to the online MLST database website (https://pubmlst.org/).

Results
The current analysis documented resistance in 77.4% of isolates for GEN, followed by 76.5% for ERY, 71.9% for TET, 58.3% for AMK, 52.2% for CIP, 50.7% for KAN, 46.1% for CLI, 29.9% for TOB, 16.2% for RIF, 14.5% for SXT, 11.6% for SYN and 11.3% for MUP. In total, 15 resistance patterns were identified, wherein
GEN, AMK, ERY (17.7%, 61/345), GEN, KAN, AMK, TET, TOB, ERY, CLI, CIP (10.1%, 35/345) and GEN, KAN, AMK, TET, ERY, CLI, CIP, SXT (8.1%, 28/345) were the top three frequently identified patterns. All the isolates were susceptible to linezolid and vancomycin. Table 1 displays the resistance pattern and distribution of samples in MRSA strains isolated from clinical sources. Isolates were distinguished into ten SCCmec types. The predominant SCCmec type was III, which included 132 isolates (38.3%), followed by type IVa (21.4%), type II (10.1%), type V (8.4%), type I (7.5%), type IVb (7.5%), type IVc (3.5%), type IVh (1.5%), type IVd (0.9%) and type XI (0.9%). Fig. 1 shows the analysis of SCCmec types based on sources of isolates.

The overall prevalence of mupirocin resistant MRSA strains was found to be 11.3%, of which 20 isolates (5.8%) had low-level mupirocin resistance and 19 (5.5%) had high-level mupirocin resistance. All MRSA strains with high-level mupirocin resistance carried the mupA gene and belonged to SCCmec types III (52.6%), II (36.9%) and I (10.5%). Fig. 2 provides summary data on the distribution resistance profiles among different SCCmec types. Analysis revealed that three isolates

**TABLE 1.** Resistance pattern and distribution of samples in 345 methicillin-resistant *Staphylococcus aureus* strains related to clinical infections

| No. of antibiotic classes | Antibiotic resistance pattern | Isolates, n (%) | Sample source (n, %) |
|----------------------------|-------------------------------|-----------------|----------------------|
| 9                          | GEN, KAN, AMK, TET, TOB, ERY, CLI, CIP, SXT | 21 (6.1)        | SW (3, 14.3), BW (6, 28.5), SuW (3, 14.3), U (9, 42.9) |
|                            | GEN, KAN, AMK, TET, ERY, CLI, CIP, RIF, SYN | 19 (5.5)        | SW (6, 31.6), B (10, 52.6), U (3, 15.8) |
|                            | GEN, KAN, AMK, TET, TOB, ERY, CLI, CIP, MUP | 15 (4.3)        | SW (10, 66.7), BW (3, 20), P (2, 13.3) |
| 8                          | GEN, KAN, AMK, TET, ERY, CLI, CIP, SXT | 28 (8.1)        | SW (4, 14.3), BW (6, 21.5), SuW (5, 17.8), B (5, 17.8), P (8, 28.6) |
|                            | GEN, KAN, TET, TOB, ERY, CIP, RIF, SYN | 15 (4.3)        | SW (3, 20), B (5, 33.3), Bf (1, 6.7), U (6, 40) |
|                            | GEN, AMK, TET, TOB, ERY, CLI, CIP, MUP | 17 (4.9)        | SW (6, 29.4), BW (9, 52.9), SuW (3, 17.7) |
|                            | GEN, KAN, AMK, TET, TOB, ERY, CLI, CIP | 35 (10.2)       | SW (7, 20), SuW (10, 28.6), B (6, 17.1), P (12, 34.3) |
| 7                          | GEN, KAN, TET, ERY, CLI, CIP, RIF | 20 (5.8)        | SW (8, 40), P (4, 20), Bf (1, 5), B (1, 5), R (6, 30) |
|                            | GEN, KAN, AMK, TET, ERY, CLI, CIP, MUP | 5 (1.5)         | SuW (4, 100) |
| 6                          | GEN, TET, ERY, CLI, CIP, MUP, TET | 4 (1.2)         | SuW (4, 100) |
|                            | GEN, TET, CIP, SXT, SYN, MUP | 1 (0.3)         | P (1, 100) |
| 4                          | GEN, KAN, TET, ERY | 17 (4.9)        | SW (6, 35.3), BW (5, 29.4), P (4, 23.5), Bf (1, 5.9), U (1, 5.9) |
|                            | GEN, TET, RIF, MUP | 2 (0.6)         | BW (1, 50), R (1, 50) |
| 3                          | GEN, AMK, ERY | 61 (17.7)       | SW (21, 34.4), BW (11, 18.1), SuW (8, 13.1), B (8, 13.1), Bf (5, 8.2), U (5, 8.2), R (1, 1.6), Rf (1, 1.6) |
|                            | GEN, TET, ERY | 7 (2)           | SW (4, 57.1), P (2, 28.6), U (1, 14.3) |
| 1                          | TET | 42 (12.2)       | SW (27, 16.7), P (7, 16.7), SuW (14, 33.3), B (4, 9.5), R (10, 23.8) |

AMK, amikacin; B, blood; BF, body fluid; BW, burn wounds; CIP, ciprofloxacin; CLI, clindamycin; ERY, erythromycin; GEN, gentamicin; KAN, kanamycin; P, purulent exudates; R, respiratory tract secretions; RIF, rifampin; SuW, surgical wounds; SW, skin wounds; SXT, trimethoprim/sulfamethoxazole; SYN, quinupristin/dalfopristin; TEC, teicoplanin; TET, tetracycline; TOB, tobramycin; U, urine.

**FIG. 1.** Distribution of SCCmec types based on isolate sources.
(0.9%) out of a total of 345 MRSA collected were positive for mecC. These mecC MRSA isolates were obtained from skin wounds (two isolates) and a burn wound (one isolate). Molecular typing showed that these isolates belonged to the clonal complex (CC)/ST130-spatype t843-agr type III (two isolates) and CC/ST599-spatype 5930-agr type I. All MRSA isolates harbouring the mecC gene carried SCCmec type XI and belonged to coa type III. The findings of the phenotypic evaluation of biofilm production in mecC MRSA isolates indicated that all isolates had strong ability to produce biofilm. The isolate belonging to CC/ST599 was positive for thetstgene. Information about characterization of the mecC MRSA isolates obtained from patients is summarized in Table 2.

Discussion

This report had several novel findings, including the first report concerning the detection of mecC MRSA in clinical samples in Iran. Strong biofilm formability with a predominance of coa type III in mecC MRSA strains was observed. A high prevalence of SCCmec type III was noted in MRSA isolates and highlights the role of these isolates in infection and outbreaks in healthcare settings. Different studies have addressed the importance and distribution of SCCmec types in understanding the origin of strains, the epidemiology and the clonal strain relatedness of MRSA [2,7,11,15].

Evidence indicates that hospital-associated (HA) and community-associated MRSA isolates may be related to different SCCmec types [3,4,15]. The distribution of SCCmec types in the 345 MRSA isolates showed that SCCmec type III was the most prevalent (38.3%), which emphasizes the nosocomial origin of these strains. This is in line with research conducted in the United States, Europe and most Asian countries [16–18]. SCCmec type III as the most prevalent cassette type was previously reported in studies conducted by Parhizgari et al. (95.7%) [17], Hashemizadeh et al. (28%) [19] and Ghanbari et al. (35.2%) [20] in Iran. According to our findings, SCCmec type III is

TABLE 2. Distribution of CCs, biofilm ability and molecular characterization of mecC-positive MRSA isolates

| Strain | Genotype | Antibiotic resistance | Resistance gene |
|--------|----------|-----------------------|-----------------|
| IR1    | 130      | GEN, KAN, AMK, TET, TOB, ERY, CL, CIP, MUP | mupA, tet(t), aac(6')-Ila, aph(3')-Ilo, msrB, erm(A) |
| IR2    | 130      | GEN, KAN, AMK, TET, TOB, ERY, CL, CIP, MUP | aac(4')-Ia, aph(3')-Ilo, tet(M), msrB, erm(C), tet(M), aac(4')-Ia, aac(6')-Ib, aph(2'), erm(C), erm(A) |
| IR3    | 599      | GEN, KAN, AMK, TET, TOB, ERY, CL, CIP, MUP | mupA, tet(M), aac(4')-Ia, aph(3')-Ilo, msrB, erm(A) |

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responsible for most of the SCCmec types in HA-MRSA infections. Therefore, it is rational to speculate that high rates of this SCCmec type in the present study could be associated with the special lineage in Iran. On the basis of our previous observations, ST239-MRSA-III was the predominant ST among the HA-MRSA strains in Iran [10,11]. This evidence leads us to conclude that HA-MRSA strains collected in present survey may be linked to the ST239 clone. Similar to other studies [15,19–21], in the present study, cassette types I and II represented a minority, with frequencies of 7.5% and 10.1% respectively. Conversely, Chongtrakool et al. [22] studied 11 Asian countries and found that the most predominant SCCmec type among MRSA strains obtained from Korea and Japan was type II.

It is worth noting that some of the researchers documented the presence of SCCmec type IV in HA-MRSA and SCCmec type III in both HA- and community-associated MRSA, indicating their transfer from the community to hospitals and vice versa [3,4,15,21]. In the current study, SCCmec typing identified 83.3% of MRSA strains as type IV. This result is supported by the findings of Valsesia et al. [21] in Switzerland, who found SCCmec type IV to be the most frequent type among HA-MRSA strains (76.6%). A low prevalence, however, was noted for SCCmec types I (5%) and II (8.3%). Although the precise reason for the presence of SCCmec type IV strains in healthcare settings is unclear and of course debatable, it is well established that the growth of MRSA isolates with SCCmec type IV is more rapid and achieves a greater infectious burden than MRSA strains with other SCCmec types; therefore, they have a selective advantage [21]. Taken together, the strong presence of MRSA-IV and the considerable multidrug resistance in our hospital confirm the hypothesis of extensive transfer from the community to hospitals. Diversity in antibiotic susceptibility profiles was more prevalent among isolates with type III SCCmec than other SCCmec types. The same results have been reported from studies conducted by Moosavian et al. [15] and Hashemizadeh et al. [19].

The current study confirmed the presence of the mecC gene in three MRSA isolates with frequencies of 0.9%. To our knowledge, this is the first report regarding the emergence of the mecC gene in clinical MRSA strains from Iran. Similar to this study, studies from Denmark [23], Switzerland [24], France [25], the United Kingdom [26], Slovenia [27], Germany [28], Austria [29], Ireland [30] and Pakistan [31] have shown the presence of mecC-positive MRSA in both animal and human samples. Unlike other studies in which mecC MRSA isolates showed universal susceptibility to non-β-lactam antibiotics [8,26,29], this study showed the multidrug resistance pattern among these isolates.

Two of the three mecC MRSA in the present research belonged to the agr type III, coa type III, spa type t843 and CC/ST130. This finding is consistent with the observations of Garcia-Álvarez et al. [7], who indicated that CC130 mecC MRSA is the most common lineage among human isolates in the United Kingdom and Denmark. Dermota et al. [27] in Slovenia analysed 395 MRSA strains isolated from different clinical samples from 2006 to 2013 and found six MRSA isolates harbouring the mecC gene, all of which belonged to CC/ST130. Dermota et al. also indicated that none of the MRSA isolates harbouring the mecC gene carried resistance genes and belonged to CC/ST130.

Although the occurrence of mecC in MRSA isolates belonging to ST399 was found to be rarely reported, we confirmed the presence of tst-positive CC/ST399 MRSA isolate harbouring the mecC gene with spa type 5930, agr type I and coa type III. Previously, the presence of CC/ST399 isolates was demonstrated in the United Kingdom, Austria, Belgium and Germany [5]. The current results regarding the toxin gene profile of ST399 isolates was similar to previously published ST399 MRSA isolates carrying the mecC gene [5,29]. This study was limited in that pulsed-field gel electrophoresis and DNA microarray techniques were not applied in the present work as a result of technical limitations.

In conclusion, this research depicted the first prevalence study of mecC MRSA in human samples in our area. This strain, however, does not seem to be highly prevalent in Iran. In this regard, routine detection approaches and molecular epidemiologic investigations of mecC MRSA are required to better understand the carriage, epidemiology and trends of this emerging human and animal pathogen.

Conflict of interest

None declared.

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