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Original Article

Microbiology Section

Isolation of *mecC* Gene carrying Methicillin Resistant *Staphylococcus aureus* in Clinical Samples from a Tertiary Care Institute, Northern India

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ABSTRACT

Introduction: The *MecC* Methicillin Resistant *Staphylococcus aureus* (MRSA) after its initial recovery in 2007 has been reported with varying frequency from different parts of the world. These isolates assume importance due to the fact that with routine testing platforms available for the detection of MRSA they can be misidentified as being methicillin sensitive which can adversely affect the treatment and outcome of infections due to MRSA harbouring the *mecC* gene.

Aim: To evaluate *mecC* gene carrying MRSA in clinical isolates.

Materials and Methods: This retrospective study was conducted in the Department of Microbiology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, India for a period of three months (May-July 2020). A total of 102 laboratory confirmed isolates of MRSA (based on biochemical tests and cefoxitin disc diffusion results) were subjected to screening for the presence of *mecA* and *mecC* gene by Polymerase Chain Reaction (PCR). Deoxyribonucleic Acid (DNA) was extracted using an in house extraction method following which *mecA* and *mecC* were amplified in a total reaction volume of 25 μL using 2x PCR master mix, 5 μL of template and 1 μL (0.4 μM final concentration) each of reverse and forward primers specific for the above mentioned genes. Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) software v24.0.

Results: All the isolates were confirmed as being methicillin resistant with 96.1% isolates carrying the *mecA* gene and 3.9% carrying the *mecC* gene. The *mecC* MRSA were recovered from pus, swab and endotracheal tip in middle aged men. One of the patient from whose sample *mecC* MRSA was recovered was suffering from hypertension, diabetes and renal faliure. MRSA exhibited high resistance to all the antimicrobial agents tested however all of them were sensitive to vancomycin and linezolid.

Conclusion: The presence of *mecC* gene in clinical isolates of MRSA is a cause of concern and calls for an extensive and continuous surveillance of such isolates as they can in future be implicated in causing severe human infections.

Keywords: Gene sequence, Gram positive pathogen, Polymerase chain reaction, Resistance

INTRODUCTION

Staphylococcus aureus a versatile Gram positive pathogen endowed with the capacity to adapt to diverse environmental conditions is responsible for causing a multitude of illnesses in human beings that affect the blood stream, skin and soft tissues, respiratory tract as well as toxin mediated illnesses etc., [1]. The emergence and worldwide dissemination of Methicillin-Resistant *S. aureus* (MRSA) has posed a major challenge in the treatment of infections caused by this organism. Resistance to methicillin in *S. aureus* is conferred by the acquisition of one of several staphylococcal cassette chromosome *mec* (SCC*mec*) elements, carrying the *mecA* gene that codes for a penicillin-binding protein homologue (PBP2a) with reduced affinity for beta-lactam antibiotics [2]. In 2007, a novel *mecA* homologue, initially named *mecA* LGA251, encoded in a new SCC*mec* element designated type XI, having ccr type 8, divergent *mecA* regulatory genes (*mecI* and *mecR*), and no joining region J3, was reported from human and bovine MRSA isolates in UK and Denmark [3]. This *mecA* homologue; subsequently named as *mecC* in 2012, exhibited only 69% identity at the DNA level and 63% identity at the protein level to the previously described *mecA*/PBP2a. Its affinity towards oxacillin was shown to be four fold that of PBP2a [3].

The *mecC* MRSA isolates assume importance given the fact that PCR as well as antigen assays carried out to detect either PBP2a or its parent gene *mecA* fail to detect them and are thus misidentified as being methicillin sensitive. This can have adverse consequences in terms of patient management and MRSA surveillance. As regards the phenotypic Antimicrobial Susceptibility Testing (AST) methods, cefoxitin has been reported to be more reliable than oxacillin in identifying the *mecC* carrying MRSA isolates [4]. Automated methods like Vitek-2 were shown to detect only 11.3% of 62 *mecC* positive isolates as resistant to both cefoxitin and oxacillin, whereas it could detect 88.7% of strains with an oxacillin susceptible/cefoxitin resistant profile [5].

Although *mecC* MRSA, was recovered in 2007, a retrospective search for such isolates in UK and Denmark went on to prove their causative role in causing infections in animals and humans way before their formal discovery [3]. The Republic of Ireland described *mecC* in human MRSA strains in 2010 [6]. In Denmark the prevalence of *mecC* MRSA among all MRSA was found to be 1.9% in 2010 that increased to 2.8% in 2011 [7]. In Germany however the prevalence of *mecC* MRSA was found to be 0.06% with no significant change between 2004-05 and 2010-11 [8]. A study in England during 2011-2012, found the prevalence of *mecC* MRSA to be 0.45% [1], whereas screening of 565 *S. aureus* isolates collected between 2005 and 2011 in western Switzerland did not identify any *mecC* carrying MRSA isolates [9]. Recently, a study from Pakistan reported the isolation of *mecC* MRSA (3%) alone and in combination with *mecA* from human samples [10]. Data on the prevalence of *mecC* carrying MRSA isolates from India is scarce which could either be due to the low prevalence of this resistance mechanism and/or problems with methods employed for *mecC* detection. An Indian study carried out to find the virulence genes

of *S. aureus* isolated from pork meat in retail outlets found that the prevalence of MRSA carrying *mecA* and *mecC* gene was 94.3 and 5.7%, respectively [11]. The present study was carried out with an aim to evaluate the existence of *mecC* in clinical isolates of *S. aureus* from a tertiary care centre in Northern India.

MATERIALS AND METHODS

This retrospective study was conducted in the Department of Microbiology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, India for a period of three months from 1st May-31st July 2020 with the preliminary aim to screen isolates of *S. aureus* for the presence of *mecC* gene. The demographic data from July 2018-December 2019 was retrieved from the medical records section of the hospital whereas the microbiological data was taken from the patient registers maintained in the laboratory. The study did not involve any patients and hence under Helsinki guidelines was exempted from ethical clearance.

S.aureus isolates were preserved as a matter of routine and were revived by inoculating into nutrient broth which was incubated overnight. These were then subcultured onto blood and nutrient agar the next day. Out of a total of 182 isolates only 102 grew and were included in the study. The samples from which these isolates had been recovered initially included blood, pus and other body fluids and respiratory samples like sputum and Bronchoalveolar Lavage (BAL) fluid. The colonies on blood and nutrient agar were identified as *S.aureus* by their characteristic morphology, gram staining, catalase and tube coagulase test [12].

Susceptibility test of the isolates was done on Muller Hinton agar by Kirby Bauer disc diffusion method. Antibiotics used were penicillin G, vancomycin, linezolid, erythromycin, clindamycin, cotrimoxazole, ciprofloxacin, cefoxitin (as a surrogate marker for methicillin resistance) and amikacin. Minimum Inhibitory Concentration (MICs) for vancomycin were noted from Vitek-2. The zones of inhibition were measured and the results interpreted according to the guidelines of Clinical Laboratory Standard Institute (CLSI) 2020 [13].

Isolates resistant to cefoxitin were presumptively identified as MRSA and further confirmed by PCR amplification of *mecA* and/or *mecC* genes.

Polymerase Chain Reaction (PCR) for the Confirmation of mecC and mecA

A total of 102 retrospective laboratory confirmed isolates of MRSA, were subjected to screening for the presence of *mecA* and *mecC* gene by PCR [11,14].

DNA extraction: An in-house method of extraction of nucleic acid combined with spin-column extraction and purification method was used. In brief, 200 μL overnight Brain Heart Infusion (BHI) broth culture of *S. aureus* was transferred to 1.5 mL Eppendorf tubes and boiled in a water bath for 15 minutes. The samples were immediately chilled in ice for five minutes and subjected to high speed centrifuge at 10,000 × g for five minutes. For removal of protein contamination and purification of the bacterial DNA, the chilled lysates were again extracted with a commercial nucleic acid extraction kit in an automated nucleic acid extraction system (QIAcube HT system, QIAGEN, GmBH, Germany) as per manufacture's protocol.

Amplification of *mecA*: Amplification of *mecA* was performed using forward primer sequence *mecA*-FP- AAAATCGATGGTAAA GGTTGGC and reverse primer sequence *mecA*-RP- AGTTCTGC AGTACCGGATTTGC, as described by Merlino J et al., [14]. PCR was performed as per the protocol described with minor modification with the following thermal cycling conditions: Initial denaturation at 95°C for 5 minutes followed by 35 cycles of amplification at 95°C for 30 seconds, 52°C for 60 seconds, 72°C for 60 seconds and final extension at 72°C for 10 minutes. PCR was performed in a total reaction volume of 25 μL using 2x PCR master mix (Promega, Madison, USA), 5 μL of template and 1 μL (0.4 μM final concentration) each of reverse and forward primers. PCR amplified a 533 bp fragment of the *mecA* specific for the PBP2 or PBP2a.

Amplification of *mecC*: For *mecC*, PCR amplification was performed using forward primer sequence *mecC*-FP- GAAAAAAA GGCTTAGAACGCCTC and reverse primer sequence *mecC*-RP- GAAGATCTTTTCCGTTTTCAGC as described previously [11]. PCR was performed in 25 μL using 5 μL of extracted DNA template, 2x PCR master mix, 1 μL of each forward and reverse primers (0.4 μM) with thermal cycling profile of initial denaturation at 95°C for 5 minutes followed by 35 cycles of amplification at 95°C for 30 seconds, 59°C for 60 seconds, 72°C for 60 seconds and final extension at 72°C for 10 minutes. PCR amplified a specific 138 bp fragment of *mecC* gene.

Control strains of *S.aureus* American Type Culture Collection (ATCC) 43300 for *mecA* positive and ATCC 25923 for *mecA* negative were used for quality control of all tests. Both *mecA* and *mecC* PCR amplified products were electrophoresed using 2% agarose gel in a horizontal electrophoresis system and visualised in a gel documentation imager (myECL imager, ThermoFisher Scientific, Waltham, USA).

Hospital record files for the 102 isolates were screened and parameters like age, gender, diagnosis at the time of admission, sample submitted, antibiotics received, duration of hospital stay and outcome in terms of death or discharge from the hospital were noted.

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS software v24.0. The data was shown in the form of frequency and percentage.

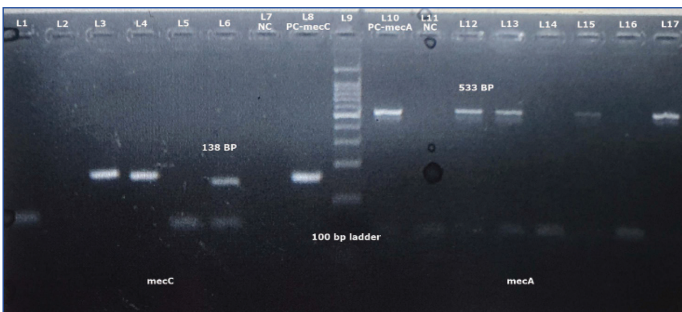
RESULTS

A total of 102 laboratory confirmed clinical isolates of MRSA that could be revived were a part of the present study. Demographic parameters, diagnosis at the time of hospital admission, duration of hospital stay, antibiotics received and outcome of the patients from whose samples MRSA were recovered is shown in [Table/Fig-1]. Out of these isolates of MRSA, *mecA* gene was found in 98 (96.1%) isolates whereas, *mecC* gene was found in 4 (3.9%) isolates as confirmed by PCR [Table/Fig-2].

Demographic and clinical parameters	*mecA* Positive MRSA n=98	*mecC* Positive MRSA n=4
Age (years)		
0-20	2 (2.1%)	0
21-40	31 (31.6%)	2 (50%)
41-60	36 (36.7%)	2 (50%)
>60	29 (29.6%)	0
Gender		
Males	63 (64.3%)	4 (100%)
Females	35 (35.7%)	0
Diagnosis at the time of hospital admission		
Gastrointestinal tract infection	3 (3.1%)	0
Respiratory tract infection	27 (27.5%)	0
Sepsis	13 (13.3%)	0
Renal failure/Liver failure	16 (16.3%)	1 (25%)
Malignancy	21 (21.4%)	0
Trauma	18 (18.4%)	3 (75%)
Duration of hospital stay		
More than 10 days	66 (67.3%)	4 (100%)
Less than 10 days	32 (32.7%)	0

Antibiotics received		
Penicillins	0	0
Cepahalosporins	34 (34.7%)	0
Penicillins+inhibitor combinations	51 (52.0%)	4 (100%)
Aminoglycosides	48 (48.9%)	4 (100%)
Tetracyclines	12 (12.2%)	0
Carbapenems	46 (46.9%)	2 (50%)
Others	21 (21.4%)	0
Outcome		
Death	2 (2.1%)	0
Discharged from the hospital	96 (97.9%)	4 (100%)

[Table/Fig-1]: Demographic profile and other parameters of the patients from whom MRSA were recovered.



[Table/Fig-2]: PCR confirmation of *S. aureus* isolates carrying the *mecA* and *mecC* genes. Lane 3, 4 and 6 are the *mecC* positive isolates (133bp) and lanes 12, 13, 15, 17 are representative *mecA* positive isolates (533bp). Lane 9 represents the 100 bp ladder, Lane 8 carries the positive control for *mecC* and Lane 10 carries the positive control of *mecA*. Lane 11 is negative control.

Two of the four *mecC* positive MRSA isolates were recovered from wound swabs that belonged to burn patients and one isolate was recovered from endotracheal tip of a patient of road traffic accident admitted in the Surgical Intensive Care Unit (SICU) of the hospital whereas one isolate was recovered from pus sample of a patient of chronic renal failure undergoing peritoneal dialysis. Samples from which MRSA isolates were recovered are shown in [Table/Fig-3]. All the *mecC* carrying MRSA were recovered from male patients in the age group of 30-49 years. Chronic renal failure patient (47-year-old male) was on peritoneal dialysis from the last five years and was suffering from hypertension and Type II diabetes mellitus. Rest of the patients did not have any co-morbidities. Road traffic accident patient was a 34-year-old male who was admitted in the SICU after undergoing surgery for his head injury. The other two patients were 39 and 42-year-old males with burn injuries to the face and chest and left thigh respectively.

Location	*mecA* MRSA n=98 (96.1%)	*mecC* MRSA n=4 (3.9%)
Blood	22 (22.4%)	-
Pus	31 (31.6%)	1 (25%)
Swab	16 (16.4%)	2 (50%)
Sputum	8 (8.2%)	-
ET aspirate	11 (11.2%)	1 (25%)
Peritoneal fluid	6 (6.1%)	-
CSF	1 (1.0%)	-
Urine	3 (3.1%)	-

[Table/Fig-3]: Samples from which MRSA isolates were recovered.

All the patients were discharged from the hospital after completion of their treatment. The antimicrobial resistance profile of all the MRSA isolates is shown in [Table/Fig-4]. All the isolates of MRSA were resistant to penicillin G and cefoxitin whereas none of the isolates were resistant to vancomycin and linezolid with variable susceptibility to other antibiotics as shown in [Table/Fig-4].

Antibiotic agents	*mecA* Positive MRSA n=98 (96.1%)	*mecC* Positive MRSA n=4 (3.9%)
Penicillin G	97 (99%)	4 (100%)
Cefoxitin	98 (100%)	4 (100%)
Erythromycin	83 (84.7%)	1 (25%)
Clindamycin	69 (70.4%)	0
Vancomycin	0	0
Linezolid	0	0
Ciprofloxacin	86 (87.8%)	1 (25%)
Amikacin	64 (65.3%)	0
Cotrimoxazole	77 (78.6%)	0

[Table/Fig-4]: Antimicrobial resistance profile of MRSA isolates harbouring the *mecA* and *mecC* genes.

DISCUSSION

In this study, the authors report for the first time the presence of *mecC* gene (3.9%) in clinical isolates of MRSA recovered from a tertiary care hospital in Jammu and Kashmir, India. The results of this study were in accordance with those reported by Khan AA et al., wherein 3% of MRSA isolates were found to harbour *mecC* gene [10]. The percentage of *mecC* MRSA that was seen in this study was however slightly more than what has been reported from various European countries so far i.e., 0.45% in England, 0.06% in Germany and 2.8% in Denmark [1,6-8]. The total number of MRSA isolates was less in the present study which could have resulted in the higher percentage of *mecC* MRSA compared to a recent meta-analysis where the prevalence of *mecC* MRSA in human subgroup was estimated to be 0.004% only [15]. The *mecC* positive MRSA isolates have been identified from different hosts across the globe with varying frequency, with most of the human case reports being described from European subcontinent, a fact that can be attributed to a robust surveillance system for the recovery of such strains [16]. In most of the case reports, *mecC* MRSA were recovered from skin and soft tissue infections [17-20]. Apart from these, *mecC* MRSA have also been recovered from blood, urine and sputum, albeit in small numbers [16]. In this study also, all the *mecC* positive MRSA isolates were recovered from pus and body fluids of patients. Two isolates were from swabs, one from ET tube and one from pus.

The patients in this study from whom *mecC* MRSA were isolated were middle aged men (30-49 years). Most of the patients described in earlier case reports were also middle-aged or elderly [6,9,17,19,20-23] except two patients: one of whom was a 34-year-old farm worker with a history of contact with animals [20], and the other a three-year-old child [17]. MRSA isolates were recovered more from male patients in a study from Pakistan with dominant age group of 18-35 years [10]. The average age of patients with *mecC* MRSA in Denmark during 2007-11 was 51 years [7] whereas in Sweden in 2005-14 it was 60 years [18].

Most of the patients in the Swedish study had some kind of underlying co-morbidity or an existing skin lesion [18]. In a study from Austria, *mecC* MRSA infections were identified in patients with primary pathologies like diabetes mellitus, myelodysplastic syndrome, peripheral arterial occlusion disease etc., [24]. Likewise in Spain *mecC* MRSA was recovered from the blood sample of a patient with urothelial carcinoma [25]. In the present study, only one patient had diabetes mellitus and hypertension. He was suffering from chronic renal failure and undergoing dialysis for the same.

All the *mecC* MRSA isolates in this study were resistant to penicillin G and cefoxitin whereas one isolate was resistant to ciprofloxacin and erythromycin each. However, the number of these isolates was too small to deduce any statistical significance. The *mecA* MRSA isolates on the other hand showed high level resistance to all the antimicrobial agents tested. All *S. aureus*

isolates were uniformly sensitive to vancomycin and linezolid. Most of the *mecC* MRSA isolates recovered form humans have shown good susceptibility for non beta-lactam antibiotics even though resistance to these antimicrobial agents has been reported in various studies [16]. Fluoroquinolone resistance was detected in two isolates in Germany [26] and in one isolate in Denmark [7] whereas macrolide and lincosamide resistance was detected in UK [27] and Sweden [18]. Norfloxacin resistance encoded by the *sdrM* gene and tetracycline resistance due to tet efflux was identified in one and two *mecC* MRSA CC130 isolates, respectively in Ireland [6,28].

Even though the origin of *mecC* MRSA is unclear, the *mecC* gene has also been detected in *Staphylococcus stepanovicii, Staphylococcus xylosus* and *Staphylococcus sciuri* suggesting that coagulase negative staphylococci could be the source of this resistance gene as was suggested for *mecA* [29]. The clinical microbiology laboratories should therefore be aware not only of *mecC* MRSA but of the possible occurrence of *mecC* in CONS as well. The *mecC* MRSA represents a relatively new form of MRSA that can colonise and cause severe fatal disease in human beings as well as wide range of other host species. For the confirmation of MRSA, molecular detection of either *mecA* by PCR or of PBP2a/ PBP2′, by antibody detection test using slide agglutination assays is considered as the gold standard [30]. Clinical laboratories using cefoxitin while performing antimicrobial susceptibility tests by disc diffusion or broth/agar dilution tests for MRSA will correctly identify strains carrying the *mecC* gene. However, problem is where either PCR targeting *mecA* or slide agglutination assays for *mecA*-encoded PBP2a are used to identify or confirm MRSA. They will misidentify *mecC* MRSA as being methicillin sensitive. The laboratories thus need to incorporate universal *mec* gene primers that are able to amplify both *mecA* and *mecC* or use *mecC* specific primers when looking for such strains.

Limitation(s)

The study was limited by its small number of *mecC* MRSA isolates, which made the comparison of various demographic and clinical parameters difficult. Differences in methodology in the studies conducted so far worldwide complicates the understanding of the true magnitude of the problem posed by *mecC* MRSA. Furthermore in the present study a detailed analysis of *mecC* MRSA isolates to delineate the clonal complexes they belong to is missing. This can better our understanding of their origin, nature and evolution in this part of the world.

CONCLUSION(S)

This was a first formal study that confirms the presence of *mecC* MRSA (3.9%) among human isolates in India. The data provides a baseline for future study and surveillance of these microorganisms. Even though the number of human *mecC* MRSA infections is low, continuous monitoring of these isolates is highly warranted given the great potential of transmissibility among different hosts which could increase the number of infection in humans due to *mecC* MRSA.

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