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Original article

Constellation of Methicillin-Resistant Genomic Islands (SCC*mec*) among Nasal Meticillin-Resistant *Staphylococcus aureus* Isolates

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SUMMARY

The apprehensiveness for the knowledge vacuum on existential threat of nasal carriage of *pvl*+ healthcare-acquired meticillin-resistant *Staphylococcus aureus* (HA-MRSA) strains amongst subjects in hospitals have led us to pursue a grasp on the constellation of staphylococcal cassette chromosome mec (SCC*mec*) types and *pvl* gene among mecA positive MRSA nasal strains. This was accomplished by phenotypic (catalase, coagulase, Microgen staph ID, ORSAB) and genotypic (polymerase chain reaction) biotyping techniques. All the mecA+ strains harboured the SCC*mec* gene; SCC*mec* type I prevailed in 43.75% and *pvl* was found in 42.1% of the isolates. Dual carriage of mecA and *pvl* genes occurred in six (37.5%, n = 6/16) strains. Overall, majority of the mecA+ MRSA strains documented in this study carried SCC*mec* elements of the HA genotype with a hint of community-acquired (CA)- genotype suggesting a possible coexistence of both HA-MRSA and community-acquired- healthcare-acquired meticillin-resistant *Staphylococcus aureus* (CA-MRSA) strains. Consequently, the implementation of methodical surveillance is needed for the evaluation of potential shifts in directionality of (HA-MRSA/CA-MRSA) *pvl*+ MRSA clones in our hospitals for effective and prudent antimicrobial stewardship.

Key words: **mecA, SCC*mec*, *pvl*, healthcare-acquired meticillin-resistant *Staphylococcus aureus* (HA-MRSA), community-acquired meticillin-resistant *Staphylococcus aureus* (CA-MRSA), *Staphylococcus aureus***

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INTRODUCTION

Acquisition of mecA gene mediates the acquisition of methicillin resistance by encoding the production of altered penicillin binding protein (PBP2a) housed on a genomic island called staphylococcal cassette chromosome mec (SCC*mec*), a mobilizable genetic element that integrates into the specific position in the chromosome (1). These elements differ in size from 20 kb to about 60 kb and are classified into types based on the orientation of mecA regulators (mecR1/mecI) and recombinases (ccrAB and ccrC) that ease SCC*mec* excision, circularization, and insertion in chromosome (2). SCC*mec* island houses the ccr complex, the mec complex and the 'Junkyard area'. The first of these cassettes (SCC*mec* I) was initially identified at the end of the 20th century in *Staphylococcus aureus*. Subsequently, two others (SCC*mec* II and III) were found from different MRSA strains (3). Contemporarily, novel types of SCC*mec* elements, like IV to XI and several new variants of already identified SCCmec types have been documented (4). Anecdotally, the lines of distinction between SCC*mec* types among community and hospitals is diminishing worldwide. The majority of hospital-acquired MRSA(HA-MRSA) and community-acquired MRSA (CA-MRSA) isolates still carry the SCC*mec* type's I–III and SCCmec types IV–V, respectively (4). Nonetheless, the carriage of SCC*mec* types IV–V is not an all-encompassing characteristic of CA-MRSA because unlike the larger mobile elements of type I to III, genomic islands IV–V are small and easily transferable which may spillover to HA-MRSA (5).

In the 20th century, Noel Panton and Francis Valentine associated a leukocyte lysing, cytolytic gamma toxin latter called Panton-Valentine leukocidin (PVL) with soft tissue infections (6, 7). Though initially disregarded and perceived to be restricted to secondary infections (8), the findings of *pvl*+ *S. aureus* (PPSA) among patients without predisposing risk factors heralded an apprehensiveness and existential discomfort amongst healthcare workers and researchers that came to the realization of its particulars and its potential effect on health care. Even with its documented epidemiological association to CA-MRSA (69 – 98%) infections, it has not been definitively proven to be a major virulence determinant for the strain (9). We caught up on literatures from previous studies that yielded conflicting results and linked the γ-hemolysin homologue with HAMRSA strains (10 – 14).

S. aureus-pvl is encoded by co-transcribed Protoxin subunits (F and S) of Panton-Valentine (PV) leukocidin (Luks) genes found in the genomes of S. aureus associated bacteriophage (8, 15, 16). The PVL toxin targets the cell membrane of leukocytes and increases its permeability (by forming pores) that leads to cellular degradation and necrosis (17, 18). In severe infections, this will result in a decrease in leukocytes count, increases in *S. aureus* virulence, responsible for intense necrotic skin infections (19, 20). The *pvl* gene is carried by methicillin susceptible (MSSA) and resistant (MRSA) *S. aureus* (7, 21). The contribution of *pvl* in musculoskeletal disorders, necrotizing pneumonia, and brain abscess has been documented. PPSA associated highly transmissible therapy-refractory skin infections, and life-threatening hemoptysis has been on the rise globally (8, 22).

The prevalence of HA-MRSA (based on mecA+ strains) in hospitals in Nigeria may differ from 1.5% to 20% (23). The purpose of this study was to determine the constellation of SCC*mec* types among mecA positive (mecA+) MRSA nasal isolates in our study center.

MATERIALS AND METHODS

Confidentiality and ethical considerations

Ethical review board of Sokoto State Ministry of Health in Nigeria approved this study (SMH/1580/V. IV). Informed consent was obtained from the study participants and information gathered were documented anonymously.

Study center, sample collection and processing

This study was conducted in three Sokoto state-owned hospitals in 2018 (Maryam Abacha Women and Children Hospital, Specialist Hospital and Orthopedic hospital Wamakko). Nasal swabs were randomly collected from 378 participants (healthcare workers, inpatients, outpatients, security men and cleaners) using commercially available swab sticks and processed as per standard microbiological procedures for the recovery of *S. aureus* (24). Biotyping for *S. aureus* was based on growth

Mannitol salt agar, Gram staining characteristics, spot tests (catalase and coagulase) and the Microgen™ Staph ID kit.

Oxacillin resistance screening agar base (ORSAB) test

A standardized suspension (0.5 McFarland) of *S. aureus* isolates were prepared and inoculated onto ORSAB medium pre-supplemented with 6 μg/ml oxacillin and 4% sodium chloride and incubated at 35^0C overnight. The emergent bluish colonies from the overnight cultures were considered methicillin resistant (25).

Polymerase chain reaction

The presumptive isolates were additionally queried by two different multiplex PCRs. The first multiplex PCR was done for the detection of methicillin resistance (mecA gene) and leukocidin toxin gene (*pvl*) (Table 1). The second multiplex PCR was done for typing SCC*mec* elements of mecA positive MRSA strains (Table 1). The primers used were calculated using Primer3Plus® based on partial coding sequences of genes of interest obtained from GenBank/NCBI (26). PCR simulation was executed using Snap Gene™ software (version 1.1.3) to determine the efficiency and the validity of the expected amplicon sizes of the proposed primers before its production (Assumption-free). Total bacterial genomic DNA was extracted from 24 hours culture on nutrient agar using the Qiagen™ DNA extraction kit (Qiagen, Hilden, Germany) in accordance with the manufacturer's protocols. The first PCR for the detection of mecA and *pvl* gene was done using the protocol given by (27) and the second PCR for the typing and subtyping of the SCC*mec* elements was carried out as follows. The reaction was performed in the final volume of 25 μL, involving 4 μL of DNA template, 12.5 μl of Qiagen master mix, 2.5 μL of Q-reagent, 0.5 μL of each primer pair (3 μL totally) and 3 μl molecular grade water. DNA was amplified with a thermocycler (Applied bio systems 9700), and multiplex PCR conditions were as follows: initial denaturation for 3 minutes at 94°C, 35 cycles of denaturation at 94°C for 40 seconds, annealing at 56°C for 45 seconds, and extension at 72°C for 1 minute. The final extension was carried out at 72°C for 4 minutes. The PCR amplicons were visualized on 1.5% agarose gel pre-stained with ethidium bromide using a 100 bp+ ladder (Bio-labs, New England, UK). They were documented with BIO-RAD gel-doc (Milan, Italy) under a UV transilluminator and analyzed with image lab™ 6.01 software (BIO-RAD, Milan, Italy) and Applied Maths Bionumerics version 7.0 (Sint-Martens-Latem, Belgium).

Table 1. *The primer sequence of the studied genes*

Primer		Sequence (5' -- > 3')	Product	Tm	Accession
SCC*mec* I	F	TCGGGTGAAAGTGATGACAC	495 bp	59.5°C	CCJ25736
	R	GCGGTAATTGATATCCAGCAA			
SCC*mec* IIa	F	TGGCGATGACGATATTGAAG	284 bp	59.65°C	AB774377
	R	ACCGCAGAAGATGACGAACT			
SCC*mec* IIb	F	AGGTTTGAAGCGGTTTTTCA	381 bp	59.72°C	AB127982
	R	CTTCTAACGCTTCGCATTCC			
SCC*mec* III	F	TCCCATATCGGAAAGAATCG	313bp	59.86°C	AB047089
	R	ACTTGCTGCATCCACTGTTG			
SCC*mec* IVa	F	TTTGAGGTTTTCGGGTGTTC	450 bp	59.95°C	AB266531
	R	TGCATGCACAGTGATAACGA			
SCC*mec* IVb	F	TGCATGCACAGTGATAACGA	1kb	59.86°C	AB063173
	R	TTTGAGGTTTTCGGGTGTTC			
mecA	F	TGGTAAAGGTTGGCAAAAAGA	533bp	59.6°C	KY788636
	R	TTGTCCGTAACCGGAATCA			
Pvl	F	TAAGGGCAAACACTTGTGGA	433bp	59.8°C	HQ020533
	R	CCATTTGATCAAGACGAGCA			

Statistical method

Descriptive statistics were used to present the study outcomes. Each study variable was compared between SCC*mec* types. Variables were summarized as proportions (%). Statistical analysis was done using SAS version 9.4 software (SAS, Cary, NC, USA).

RESULTS

We studied eighty-one phenotypic *S. aureus* nasal isolates from state-owned hospitals and arrived at thirty-eight phenotypically confirmed MRSA strains out of which 16 were PCR- positive for mecA and 17 for *pvl* gene (Figure 1). Dual carriage of mecA and *pvl* occurred in six (37.5%, n = 6/16) strains. The isolates were resolved into four clades: A, B, C and D with decreasing PCR profile similarity. Cluster A housed mecA+-*pvl*+ strains. Clade B comprised mecA+ stains, C housed *pvl*+ and D was PCR-negative. Further, we amplified SCC*mec* from all strains (100%) that were PCR-positive for the mecA gene (Figure 2). SCC*mec* type I prevailed in 43.75%, type IIA in 18.75%, type IIB in 12.50%, type

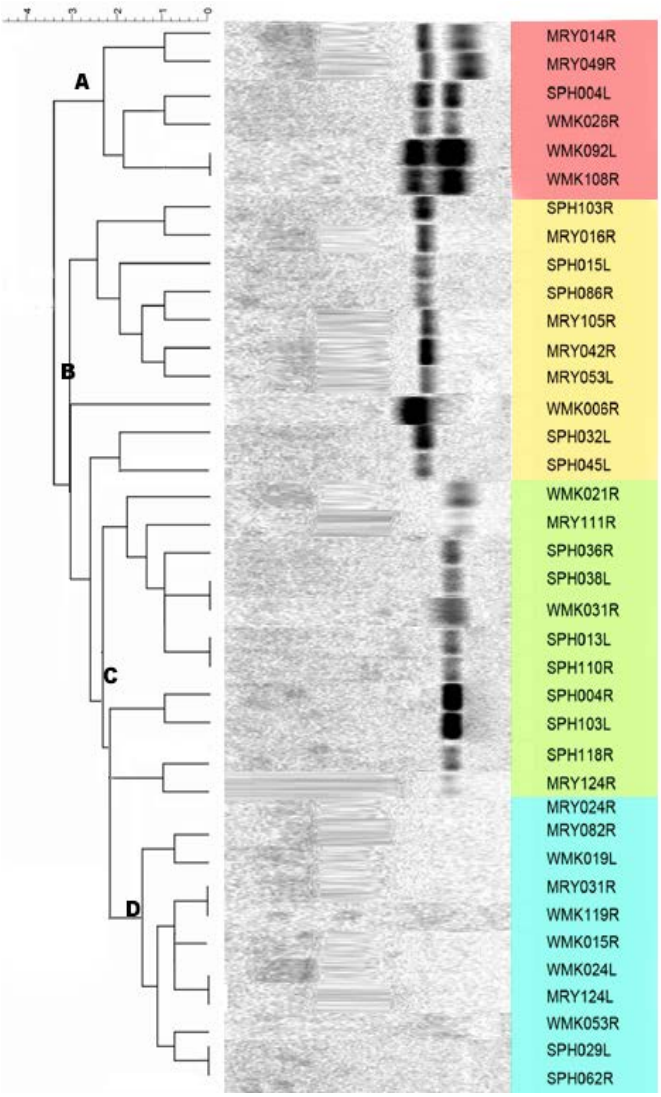


Figure 1. *A clustering tree of DNA gel fingerprint resolved from electropherograph showing MRSA strains segregated based on their SCCmec type in groups of various sizes. In the figure, clustering identified four clades based on banding profiles; a scale bar indicates a degree of similarity. Note: Red = PCR-positive for dual carriage of mecA and pvl; Yellow = PCR-positive for mecA only; Green = PCR positive for pvl gene only, and Blue = PCR negative strains.*

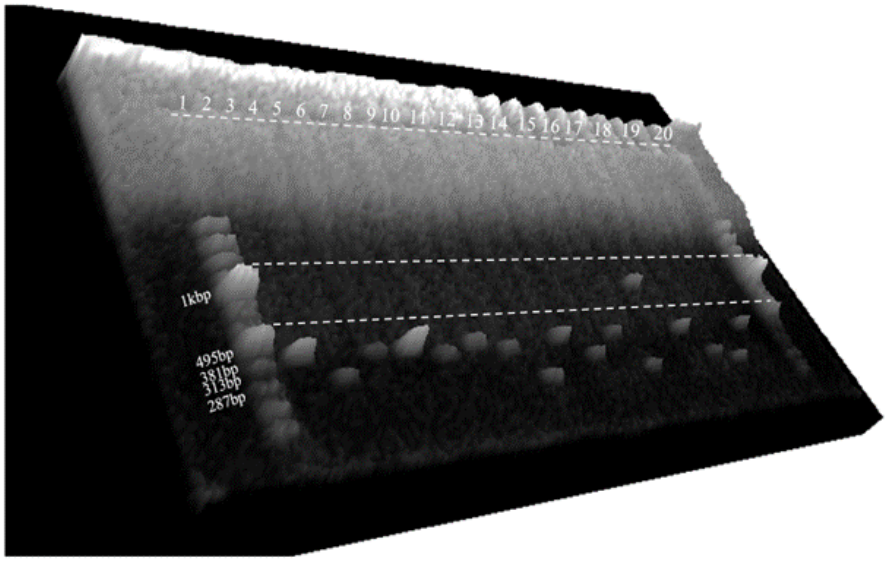
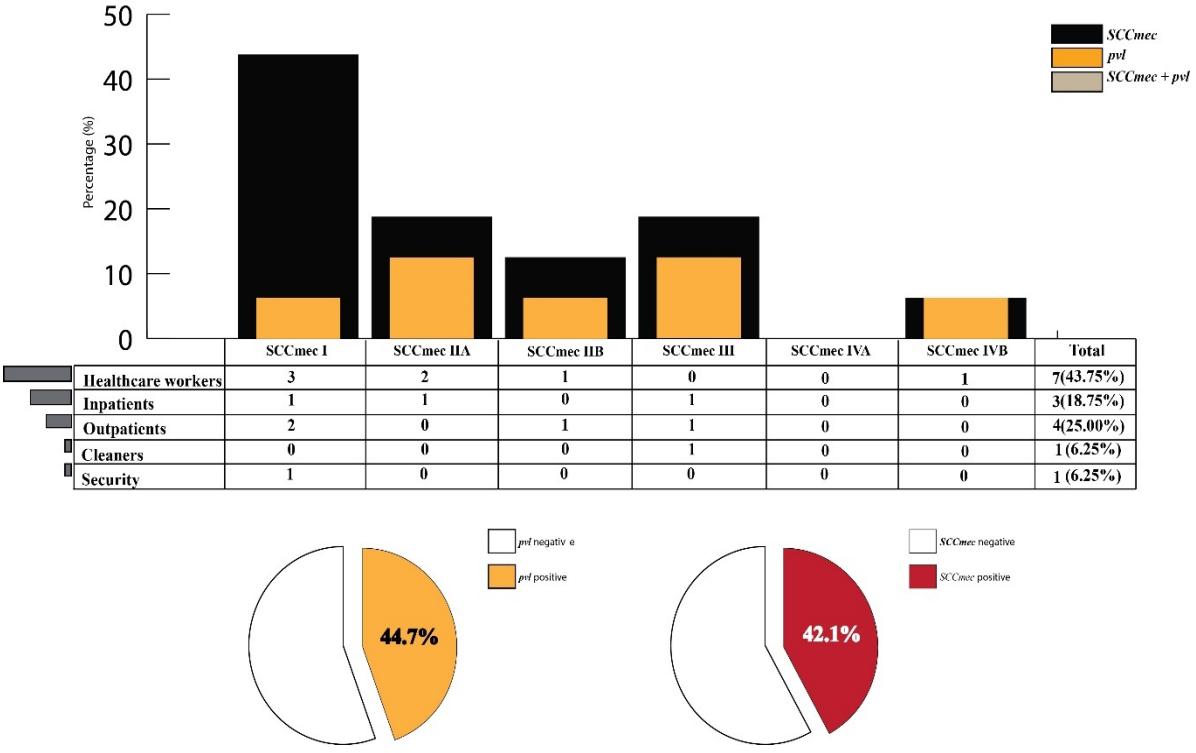


Figure 2. *Three-dimensional electrophoretogram of ethidium bromide-stained gel showing amplification of SCCmec I (495 bp), SCCmec IIa (284 bp), SCCmec IIb (381 bp), SCCmec III (313 bp), SCCmec IVa (450bp), and SCCmec IVb (1kb) from 16 mecA positive MRSA strains. In the figure, Lane 1 and 20 = 100 bp+ DNA ladder, Lane 2 = S. aureus ATCC 25923 (Positive control), Lane 3 - 18 = Contain all 16 MRSA strains and Lane 19 = Negative control (Nuclease-free water)*



	SCCmec I	SCCmec IIA	SCCmec IIB	SCCmec III	SCCmec IVA	SCCmec IVB	Total
Healthcare workers	3	2	1	0	0	1	7(43.75%)
Inpatients	1	1	0	1	0	0	3(18.75%)
Outpatients	2	0	1	1	0	0	4(25.00%)
Cleaners	0	0	0	1	0	0	1 (6.25%)
Security	1	0	0	0	0	0	1 (6.25%)

Figure 3. *Percentage distribution of SCCmec and pvl genes of mecA positive MRSA strains*

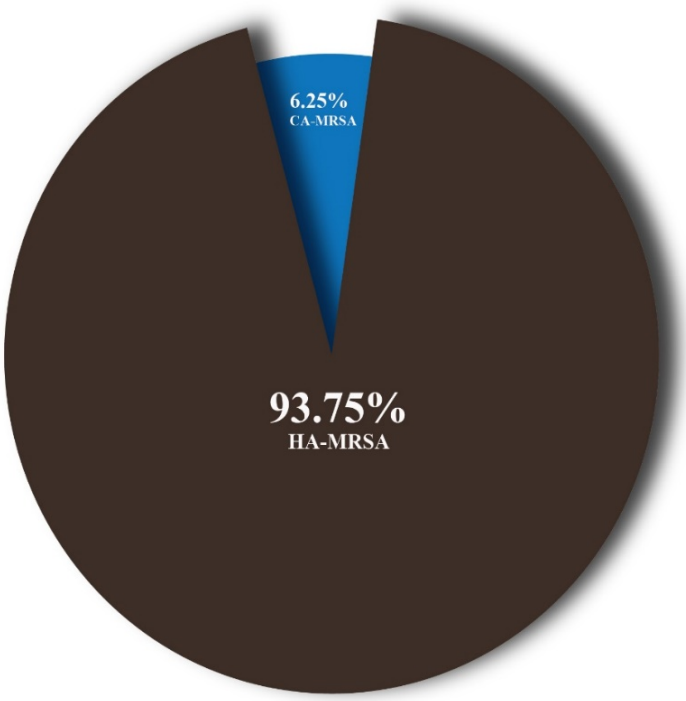


Figure 4: *Distribution of HA-MRSA and CA-MRSA strains amongst mecA positive strains*

III in 18.75% and type IVA in 6.25% of the MRSA isolates. None of the isolates were typable for SCC*mec* type IVA (Figure 3). The *pvl* gene was documented in 6.25% of stains typed SCC*mec* I, IIB and IVB, and 12.5% of SCC*mec* IIA and III typed strains. Overall, the prevalence of SCC*mec* and *pvl* gene was 42.1% and 44.7%, respectively. We encountered SCC*mec* gene among healthcare workers (43.75%), inpatients (18.75%), outpatients (25%), cleaners (6.25%) and security men (6.25%). Most of the mecA positive isolates that harbored both SCC*mec* gene and *pvl* genes originated from healthcare workers and inpatients. Almost all the mecA+ strains were HA-MRSA (Figure 4).

DISCUSSION

In this work, we provided genotypic data on 38 phenotypic MRSA strains discovered during a six-month period in Sokoto state-owned hospital in order to elucidate the genetic pool and potential emergence of unexpected MRSA strains. The mecA carrying MRSA strains prevailed in 42.1% of phenotypic methicillin resistant strains amongst the hospital with a 93.75% presence of HA-MRSA. This prevalence of HA-MRSA strains carrying a HA genotype in this study was higher than previous rates reported by Okwu et al. (28), Ghebremedhin et al. (29), Pathare et al. (30), Mohajeri et al. (31), and Parvez et al. (32) that documented the occurrence rates of 59%, 52.85%, 15.1%, 36.8% and 40%, respectively.

A pertinent proportion of mecA positive MRSA strains with HA genotype was associated with healthcare workers carrying SCC*mec* I, II, and III confirming that most of carried strains emerged from health care settings. Possible reasons for the assortment of SCC*mec* type might be due to differences in geographical regions, the study population, and detection methods. SCC*mec* types IVB was rare and carried by 6.25% of the strains. This cassette type is traditionally attributed to CA-MRSA (10, 33). Our result is dissident with those documented by mathematical models that posited the replacement of traditional HA-MRSA strains by CA-MRSA strains, due to their higher growth rate and greater fitness (3), but conforms with the models that hospital-community interactions provoke coexistence among methicillin resistant strains of *S. aureus*. (34 – 36). HA and CA strains of MRSA can coexist if the wider resistance range of the HA strains is balanced by transitional fitness-disadvantages in the presence of resistant strains. The HA strains are better selected in the hospital, where antibiotics are regularly used, but community-associated strains thrive (higher fit-

ness) in the community where the use of antibiotics is relatively low (opposite directions of selection) (34). Despite conflicting directions of selection, these strains exist in both settings because of the high rates of hospitalization and discharge, which rotates individuals between the hospital and the community. Besides, our results also specify that opposite directions of selection are not adequate for maintaining coexistence (34).

The carriage of *pvl* gene (*pvl*+) in 44.7% of MRSA isolates in this report is consistent with 58.8% reported by Govindan et al. (37) and in dissidence with reports from Nigeria (16%) (38), Egypt (2.2%) (39), Uganda (73%) (40). In our study, among the tested mecA+ MRSA isolates, *pvl*+ was chiefly associated with HA genotype (37.5%). Previous studies have recognized that the *pvl* genes are carried mostly by CA-MRSA (41, 42). Paradoxically, *pvl*-carrying HA-MRSA strains have also been previously described (23).

Lastly, this study had a few limitations. First, the study was conducted in a few healthcare centers and may have biased the representativeness of the isolates herein studied. Second, clinical features were not considered in characterizing both CA-MRSA and HA-MRSA. We used only genotypic characteristics to classify MRSA.

CONCLUSION

Overall, majority of MRSA recovered in our study centres carried diverse SCC*mec* elements of the HA genotype with a hint of CA- genotype. We documented the dominance HA-MRSA-*pvl*+. Our data also revealed the presence of CA-MRSA strains suggesting a possible coexistence of both HA-MRSA and CA-MRSA strains. Consequently, implementing methodical surveillance is needed for the evaluation of shift in directionality of (HA-MRSA/CA-TOXNMRSA) *pvl*+ clones in our hospitals for effective and prudent antimicrobial stewardship.

Conflict of interest

All authors declare to have no conflict of interest.

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Konstelacija genomskih ostrva (SCC*mec*) rezistentnih na meticilin kod nazalnih izolata *Staphylococcusa aureusa* rezistentnog na meticilin

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SAŽETAK

Zabrinutost zbog vakuuma u znanju o egzistencijalnoj opasnosti nazalnog nosilaštva *pvl*+ HA-MRSA sojeva kod hospitalizovanih navela nas je da bolje istražimo konstelaciju SCC*mec* tipova i *pvl*-gena kod mecA pozitivnih sojeva u slučaju nazalnog kliconoštva meticilin-rezistentnog *Staphylococcusa aureusa*. Iz ovog razloga urađene su fenotipske (catalaza, coagulaza, Microgen staph ID, ORSAB) kao i genotipske (lančana reakcija polimeraze) tehnike biotipizacije. Svi mecA+ sojevi sadržali su SCC*mec* gen; SCC*mec* tip I preovladavao je kod 43,75% izolata, a *pvl* kod 42,1% izolata. Dualno nosilaštvo mecA i *pvl* gena zabeleženo je kod 6 (37.5%, n = 6/16) sojeva. Većina mecA+ MRSA sojeva registrovanih u ovoj studiji nosili su SCC*mec* elemente HA genotipa sa naznakom CA- genotipa, što je ukazivalo na moguću koegzistenciju HA-MRSA i CA-MRSA sojeva. Kao rezultat ovoga, uvođenje metodičnog nadzora potrebno je zbog procene mogućih promena usmerenosti (HA-MRSA/CA-MRSA) *pvl*+ MRSA klonova u našim bolnicama kao i efikasnog i pažljivog praćenja antimikrobnih lekova.

Ključne reči: **mecA, SCC*mec*, *pvl*, HA-MRSA, CA-MRSA, *Staphylococcus aureus***