Arch Clin Infect Dis. 2023 October; 18(5):e139695. https://doi.org/10.5812/archcid-139695.

Published online 2023 November 22. **Research Article**

First Report of the Emergence of *mecC* Gene and CC8/ST239 Tigecycline-Resistant *Staphylococcus aureus* Clonal Lineage Isolated from Chronic Suppurative Otitis Media

Chakameh Amini [1, 2], Zahra Rahmani [3], Sareh Sadat Hosseini [1], Parmida Bagheri [4] and Mehdi Goudarzi [1, *]

[1]Department of Microbiology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Biology, North Tehran Branch, Islamic Azad University, Tehran, Iran
[3]Department of Otorhinolaryngology, Loghman Hospital, Shahid-Beheshti University of Medical Sciences, Tehran, Iran
[4]Department of Biotechnology, Faculty of Life Sciences and Biotechnology, Shahid Beheshti University, Tehran, Iran

[*]*Corresponding author*: Department of Microbiology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: gudarzim@yahoo.com

Received 2023 August 04; **Revised** 2023 October 29; **Accepted** 2023 October 31.

Abstract

Background: *Staphylococcus aureus* is one of the most significant bacteria involved in ear infections. However, insights into the molecular attributes of *S. aureus* collected from patients with chronic otitis media have yet to be reported in Iran.
Objectives: The objective of this study was to assess the molecular characteristics of *S. aureus* isolated from patients with chronic otitis media.
Methods: A total of 55 *S. aureus* strains retrieved from patients with chronic otitis media were analyzed by the disk diffusion method and polymerase chain reaction (PCR) to identify the *nucA* gene. Isolates were genetically classified using the coagulase typing method. *S. aureus* protein A (*spa*) typing, staphylococcal cassette chromosome *mec* (SCC*mec*) typing, and multilocus sequence typing (MLST) were performed on isolates with resistance to specific antibiotics.
Results: Overall, out of 55 *S. aureus* isolates, resistance to mupirocin, fusidic acid, and tigecycline was identified in 12.7%, 5.4%, and 3.6% of isolates, respectively. Fusidic acid-resistant isolates belonged to ST5-SCC*mec*II/t002/*coa*II. Two tigecycline-resistant isolates belonged to CC8/ST239-SCC*mec*III/t234/*coa*VIII. One positive *mecC* isolate belonged to the CC/ST130-SCC*mec*XI/t843/*coa*III clone. Isolates with the iMLSB phenotype belonged to CC/ST80-SCC*mec*IV/t044/*coa*II (4 isolates), CC8/ST239-SCC*mec*III/t388/*coa*VI (3 isolates), and CC8/ST8-SCC*mec*IV/t008/*coa*III (1 isolate).
Conclusions: Our results indicated that *S. aureus* isolated from patients with chronic otitis media possesses a unique molecular profile with a high percentage of resistance to multiple medications. These findings suggest that resuming the molecular analysis to improve the control and prevention of ear infections related to *S. aureus* is necessary.

Keywords: *Staphylococcus aureus*, Otitis Media, Methicillin-Resistant *Staphylococcus aureus*, Multilocus sequence Typing, Multidrug Resistance

1. Background

Chronic suppurative otitis media (CSOM) is characterized by middle ear effusion without symptoms of acute inflammation. According to the evidence, a high incidence of CSOM was reported in the developing countries. The CSOM is mainly caused by bacterial middle ear infection (1). Some studies indicated *Pseudomonas aeruginosa* as the prevalent cause of CSOM, while other researchers displayed *Staphylococcus aureus* as the most important bacteria. In recent decades, simultaneous resistance to multiple drugs in *S. aureus* isolated from CSOM has become a severe threat to global health (2, 3). As methicillin use increases, methicillin-resistant *S. aureus* (MRSA) is increasingly reported. Methicillin resistance is mediated by *mecA* and much less by *mecC* (4). Up to now, several molecular typing methods have been employed for genotyping *S. aureus* strains, including pulsed-field gel electrophoresis, staphylococcal cassette chromosome *mec* (SCC*mec*) typing, *agr* typing, protein A gene (*spa*) typing, multilocus sequence typing (MLST), and coagulase gene (*coa*) typing (4, 5). The *coa* typing is a multiplex polymerase chain reaction (PCR)-based method that is cost-effective,

rapid, easily interpretable, and appropriate for identifying the genetic relationships among *S. aureus* isolates (5). Only a few studies are available worldwide addressing the genotyping of *S. aureus* isolated from ear infections (3). In Iran, several studies have focused on the occurrence and phenotypic characteristics of *S. aureus* isolated from ear infections, but little data has been published on the genetic variability of these isolates (6-8).

2. Objectives

The current research was designed to evaluate the antimicrobial resistance profile and molecular characteristics of *S. aureus* isolates for CSOM based on *coa* gene polymorphism analysis.

3. Methods

3.1. S. aureus Identification

This research was carried out during January 2020 to December 2022 in a teaching hospital of Shahid Beheshti University of Medical Sciences, Iran. Informed consent was received from all participants. Purulent discharge was collected from the middle ear via a sterile swab. The patients had not taken any antibiotics for three weeks prior to the visit and had no history of hospitalization. The collected purulent swabs were immediately cultured on blood agar (HiMedia, Mumbai, India) and preliminarily recognized as *S. aureus* by routine techniques. All phenotypically confirmed *S. aureus* isolates underwent PCR for the *nuc* gene detection and final confirmation (9).

3.2. Antibiotic Sensitivity Test

Susceptibility to ten antibiotic disks (Oxoid Ltd, Basingstoke, Hampshire, UK), including gentamicin (GEN), erythromycin (ERY), fusidic acid (FUS), ciprofloxacin (CIP), rifampin (RIF), penicillin (PEN), clindamycin (CLI), tetracycline (TET), and linezolid (LIN) was carried out by the Kirby-Bauer method. The results were interpreted following the Clinical and Laboratory Standards Institute (CLSI) guideline. The cefoxitin (30 μg) disc diffusion test on Mueller Hinton agar plates was performed for all isolates of *S. aureus* to screen MRSA isolates. Each run was performed with the reference strains of *S. aureus* ATCC 25923, ATCC 43300, and ATCC 29213 as control strains. Broth microdilution was used to confirm resistance to vancomycin (VAN), tigecycline (TIG), and mupirocin (MUP) [low-level (LLMUPR) and high-level (HLMUPR) mupirocin resistance] (Sigma-Aldrich, St. Louis, Mo) following the CLSI criteria. D-zone was examined to identify inducible clindamycin resistance phenotype ($iMLS_B$; inducible macrolide-lincosamide-streptogramin B). Multidrug resistance (MDR) in *S. aureus* strains was defined as resistance to 3 $\geq$ classes of antibacterial agents, as explained earlier (10, 11).

3.3. Detection of Resistance and Toxin-encoding Determinants

After the genomic DNA extraction using the phenol-chloroform technique, isolates were screened for the existence of the toxin genes, including *pvl, eta, etb*, and *tst*, by PCR (10, 12). The *mupA, fusA, mecC*, and *mecA* genes were detected by PCR as described elsewhere (4).

3.4. Molecular Typing

A multiplex PCR-based method with four sets (A-D) was used to analyze the *coa* types (I-X) with specific primers and PCR conditions introduced by Hirose et al. (5). All isolates were characterized by *coa* typing while *S. aureus* protein A (*spa*) typing, staphylococcal cassette chromosome *mec* (SCC*mec*) typing, and multilocus sequence typing (MLST) was performed on the *mecC*-positive, fusidic acid, tigecycline, and mupirocin-resistant isolates according to the same conditions published earlier (11).

4. Results

The current research investigated 55 *S. aureus* strains obtained from CSOM cases. Of all participants, 21 (38.2%) were male and 34 (61.8%) were female, and the mean age was 28 years (range: 12 - 58 years). All the isolates were confirmed as MRSA. According to the disk diffusion test, the highest levels of resistance were recorded for penicillin (100%) and tetracycline (80%), followed by gentamicin (69.1%), ciprofloxacin (54.5%), erythromycin (50.1%), clindamycin (36.4%), and rifampin (25.5%). All tested strains showed susceptibility to vancomycin and linezolid. In our study, 13 resistance patterns were detected, wherein PEN, GEN, TET, ERY, CLI, CIP, RIF (18.2%; 10/55), PEN, GEN, ERY, TET, CLI (14.5%; 8/55), and PEN, GEN, TET (12.7%; 7/55) were the top three frequently identified profiles. Broth dilution test indicated that 12.7%, 5.4%, and 3.6% of isolates were resistant to mupirocin, fusidic acid, and tigecycline, respectively. Among mupirocin-resistant isolates, HLMUPR and LLMUPR phenotypes were detected at 3.6% and 9.1%, respectively. The susceptibility test showed that 8 isolates (14.5%) were confirmed as $iMLS_B$ phenotypes. Moreover, among the tested isolates, 27.3% (15/55) were toxigenic. The *pvl* gene (18.2%) was recovered the most, followed by the *tst* gene (9.1%), and according to the multiplex PCR test for *coa* typing of 55 tested isolates, type III had the highest prevalence, representing 36.4%,

followed by types IVb (18.2%), VIII (14.5%), II (10.9%), X (9.1%), VI (7.3%), and I (3.6%) (Table 1). Two strains of HLMUPR-MRSA were found to harbor the *mupA* gene and belonged to the CC8/ST239-SCC*mec*III/t037 lineage. The LLMUPR-MRSA strains belonged to the CC/ST22-SCC*mec*IV/t790/*coa*III (60%; 3/5) and ST15-SCC*mec* IV/t084/*coa*III (40%; 2/5) clones. All 3 fusidic acid-resistant MRSA isolates exhibited fusidic acid MIC values of $\geq$ 64 μg/mL, carried the *fusA* gene, and belonged to the ST5-SCC*mec* II/t002/*coa*II clone. Analysis of 2 tigecycline-resistant isolates indicated that they belonged to the CC8/ST239-SCC*mec*III/t234/*coa*VIII clone. Present data displayed that one isolate belonging to CC/ST130-SCC*mec*XI/t843/*coa*III was positive for *mecC*. Furthermore, isolates with $iMLS_B$ phenotype belonged to the CC/ST80-SCC*mec*IV/t044/*coa*II (4 isolates), CC8/ST239-SCC*mec*III/t388/*coa*VI (3 isolates), and CC8/ST8-SCC*mec*IV/t008/*coa*III (1 isolate) clones.

5. Discussion

The present study revealed that the incidence of fusidic acid resistance was 5.4%, harboring *fusA*, and belonged to the ST5-SCC*mec* II/t002/*coa*II clone. This percentage is lower than the reported rates in other countries, such as Ireland (19.9 %) (13), Kuwait (9.3%), and Germany (10.3%) (13, 14). In a meta-analysis in 2021, the low prevalence rate of fusidic acid resistance was noted in *S. aureus* isolates (0.5%). The incidence of fusidic acid-resistant *S. aureus* isolates was different in the earlier investigations performed in Iran by Zamani et al. (8.3%) (9), Goudarzi et al. (2.5%) (15), Rahimi et al. (3%) (16), and Hasani et al. (3.7%) (17). The higher prevalence rate of fusidic acid resistance in the present study compared to the earlier reports in Iran may be related to the unrestricted prescription of fusidic acid, use of this antibiotic during the initial treatment without susceptibility testing, diverse attitudes towards antimicrobial protocols, and the circulation of fusidic acid-resistant types within the hospitals. Similar to our findings, Chen et al. in Taiwan found that the most prevalent type of fusidic acid-resistant *S. aureus* strains was found to be ST5-SCC*mec*II/t002 (29%) and ST239-SCC*mec*III/t037 (62%) (18). The same research by den Heijer et al. reported the presence of t002 and t005 types carrying *fusA* in fusidic acid-resistant *S. aureus* strains from nine European countries (19). It can be concluded that the common lineages of *S. aureus* strains resistant to fusidic acid may be circulating from country to country. Therefore, a molecular epidemiological map of these isolates should be supervised worldwide.

Resistance to mupirocin among MRSA strains is increasing and is now recognized as a worldwide problem. The results of this research demonstrated the incidence rate of mupirocin resistance in 12.7% of MRSA isolates (HLMUPR 3.6%; LLMUPR 9.1%). The prevalence rate of mupirocin-resistant MRSA varied in different countries, such as 27.8% in South Africa, 12.1% in Canada, 31.3% in the USA, 45.5% in Turkey, and 39.6% in Iran (20). The prevalence of HLMUPR-MRSA in this study was found to be greater than that reported in France (0.8%), Canada (4.3%), and China (7%) (21-23). The present research corroborates the findings of Goudarzi et al. who reported that HLMUPR *S. aureus* strains belonged to ST8-SCC*mec*IV (27.4%), ST5-SCC*mec*IV (9.8%), and ST239-SCC*mec*III (7.8%), while the ST22-SCC*mec*IV/t790 (21.6%), ST239-SCC*mec*III/t860 (17.7%), and ST15-SCC*mec*IV/t084 (15.7%) clones were linked to the LLMUPR phenotype (10). The ST239-SCC*mec* III clone was also reported in HLMUPR *S. aureus* strains reported from India and Kuwait (24, 25).

The present study revealed an occurrence rate of *mecC* in 1.8% of MRSA isolates. In line with findings from previous research, this gene has been detected in *S. aureus* in Pakistan (26), Austria (27), Slovenia (28), and Switzerland (29). Similar to our findings, CC/ST130-SCC*mec*XI/t843 carrying the *mecC* gene was also reported earlier in the UK and Denmark as the most prevalent carrying *mecC* clone among clinical strains (30). In addition, Dermota et al. in Slovenia reported a prevalence of 1.5% for this gene in MRSA isolates possessing the *mecC* gene belonging to CC/ST130 (28). In our earlier research, CC/ST599 was reported as a *mecC*-positive *S. aureus* isolate (4).

In this study, we found two tigecycline-resistant isolates (3.6%). Different findings were reported in Malaysia (5.5%) (31), Libya (3.6%) (32), and Iran (6.6%) (33). Furthermore, some studies have documented the presence of *mecC* in MRSA strains recovered from Taiwan, Germany, China, Italy, Canada, France, Nigeria, and Poland (34). It can be inferred that inadequate governance of antibiotic administration strategies, improper policies, and extensive use of antibiotics, which likely increase the chance of genetic variations and acquisition of tigecycline-resistance genes, may be different causes for the emergence of tigecycline-resistant MRSA isolates. For all these reasons, the high prevalence and genetic variability of tigecycline-resistant MRSA isolates might also pose a severe risk to public health, suggesting the need for further attention to the detection and genetic diversity of these isolates. Our results indicated that all MRSA isolates resistant to tigecycline belonged to the CC8/ST239-SCC*mec*III/t234/*coa*VIII clone. In a similar study in Brazil, Dabul and Camargo identified *S. aureus* strains resistant to tigecycline belonging to the ST105-SCC*mec*II clone (35). Nonetheless, CC8/ST239 clone resistance to tigecycline has been reported in *S. aureus* from Switzerland, Spain, UK, Kuwait, Japan, Australia, and

Table 1. Characteristics of the 55 MRSA Strains Obtained from CSOM Cases

coa Type	Toxin Genes, No. (%)	Antibiotic Resistance Profile (No; %)	Total, No. (%)
I	-	PEN, TET, CIP (1; 50)	2 (3.6)
		PEN, GEN, ERY, TET, CIP (1; 50)	
II	*pvl* (3; 37.5)	PEN, GEN, ERY, TET, CLI (2; 33.3)	6 (10.9)
		PEN, GEN, TET, FUS (2; 33.3)	
		PEN, GEN, TET (1; 16.7)	
		PEN, TET, FUS (1; 16.7)	
III	*pvl* (5; 25), *tst* (2; 10)	PEN, GEN, ERY, TET, CLI, RIF, CIP (6; 30)	20 (36.4)
		PEN, GEN, ERY, TET, CLI (3; 15)	
		PEN, GEN, ERY, CIP, MUP (3; 15)	
		PEN, GEN, TET, MUP (2; 10)	
		PEN, GEN, ERY, CLI, RIF, CIP, MUP (2; 10)	
		PEN, TET, CIP (4; 20)	
IVb	*tst* (2;20)	PEN, GEN, ERY, TET, CIP (2; 20)	10 (18.2)
		PEN, TET, CIP (4; 40)	
		PEN, GEN, TET (2; 20)	
		PEN, GEN, ERY, TET, CIP (2; 20)	
VI		PEN (4; 100)	4 (7.3)
VIII	*tst* (1; 12.5)	PEN, GEN, TIG, RIF (1; 12.5)	8 (14.5)
		PEN, TET, TIG, RIF (1; 12.5)	
		PEN (1; 12.5)	
		PEN, GEN, ERY, TET, CLI, RIF, CIP (2; 25)	
		PEN, GEN, ERY, TET, CLI, (2; 25)	
		PEN, GEN, TET (1; 12.5)	
X	*pvl* (2; 40)	PEN, TET, CIP (1; 20)	5 (9.1)
		PEN, GEN, TET (1; 20)	
		PEN, GEN, ERY, TET, CLI, (1; 20)	
		PEN, GEN, ERY, TET, CLI, RIF, CIP (2; 40)	

China (34).

This study found a low to moderate prevalence of isolates with iMLSB phenotype (14.5%). Different rates have also been reported from *S. aureus* isolates from Iran (10.9%) (11), Jordan (76.7%) (36), Nepal (21%) (37), and Brazil (7.9%) (38), which suggested that it might be a remarkable phenomenon influenced by the excessive usage of macrolides, regional locations of the study population, infection prevention protocols in healthcare facilities, and the prior history of antibiotic usage in patients. In the present study, the iMLSB phenotype (14.5%) belonged to the CC/ST80-SCC*mec*IV/t044 (4 isolates), CC8/ST239-SCC*mec*III/t388 (3 isolates), and CC8/ST8-SCC*mec*IV/t008 (1 isolate) clones. The CC8 clone is described to be a prevalent iMLSB phenotype MRSA in Iran (11). In addition, Goudarzi et al. reported that isolates with iMLSB phenotype were observed in CC88/ST239 (13.3%), CC/ST22 (4%), and CC/ST30 (4%) clonal lineages (12).

5.1. Conclusions

Our study on the molecular characterization of *S. aureus* obtained from CSOM cases indicates the occurrence of MDR *S. aureus*, which significantly limits the availability of effective antimicrobial treatments. These findings confirmed the dissemination of specific clonal lineages in *mecC*-positive, inducible, mupirocin- and tigecycline-resistant *S. aureus* strains. Further investigation into these emerging clones would improve understanding of the molecular epidemiological map and their resistance profile trends. Future studies that

monitor the genetic diversity of lineages and their prevalence among similar populations are required.

Footnotes

Authors' Contribution: CH. A. conceived and designed the study and drafted the manuscript. M. G. participated in designing the study, performed parts of the statistical analysis, and helped to draft the manuscript. Z. R. re-evaluated the clinical data, revised the manuscript, performed the statistical analysis, and revised the manuscript. P. B. collected and interpreted the clinical data and revised the manuscript. All authors read and approved the final manuscript.

Conflict of Interests: The authors have no conflict of interest.

Data Reproducibility: The dataset presented in this study is available on request from the corresponding author during submission or after publication. The data are not publicly available due to maintaining confidentiality.

Ethical Approval: This study was approved by the Ethics Committee of the Shahid Beheshti University of Medical Sciences in Tehran, Iran, under the ethical code of IR.SBMU.MSP.REC.1401.366.

Funding/Support: This work was supported by a fund from the Research Deputy of Shahid Beheshti University of Medical Sciences, Tehran, Iran (Grant No. 43003263). The funding agency has no role in the design of the project, work execution, analyses, interpretation of the data, manuscript writing, and submission.

Informed Consent: Informed consent was received from all participants.

References

1. Dhingra S, Vir D, Bakshi J, Rishi P. Mapping of audiometric analysis with microbiological findings in patients with chronic suppurative otitis media (CSOM): A neglected clinical manifestation. *Crit Rev Clin Lab Sci*. 2023;**60**(3):212–32. [PubMed ID: 36604829]. https://doi.org/10.1080/10408363.2022.2158173.
2. Kawatra R, Pandey S, Agarwal A, Tholia J. Evaluation of the Current Bacterial Pathogens and Antibiogram of Chronic Suppurative Otitis Media in Adults. *Indian J Otolaryngol Head Neck Surg*. 2023;**75**(4):3072–6. [PubMed ID: 37974803]. [PubMed Central ID: PMC10645890]. https://doi.org/10.1007/s12070-023-03904-0.
3. Choi HG, Park KH, Park SN, Jun BC, Lee DH, Yeo SW. The appropriate medical management of methicillin-resistant Staphylococcus aureus in chronic suppurative otitis media. *Acta Otolaryngol*. 2010;**130**(1):42–6. [PubMed ID: 19424918]. https://doi.org/10.3109/00016480902870522.
4. Goudarzi M, Navidinia M, Dadashi M, Hashemi A, Pouriran R. First report of methicillin-resistant Staphylococcus aureus carrying the mecC gene in human samples from Iran: prevalence and molecular characteristics. *New Microbes New Infect*. 2021;**39**:100832. [PubMed ID: 33425366]. [PubMed Central ID: PMC7777544]. https://doi.org/10.1016/j.nmni.2020.100832.
5. Hirose M, Kobayashi N, Ghosh S, Paul SK, Shen T, Urushibara N, et al. Identification of staphylocoagulase genotypes I-X and discrimination of type IV and V subtypes by multiplex PCR assay for clinical isolates of Staphylococcus aureus. *Jpn J Infect Dis*. 2010;**63**(4):257–63. [PubMed ID: 20657065].
6. Mofatteh MR, Shahabian Moghaddam F, Yousefi M, Namaei MH. A study of bacterial pathogens and antibiotic susceptibility patterns in chronic suppurative otitis media. *J Laryngol Otol*. 2018;**132**(1):41–5. [PubMed ID: 29151379]. https://doi.org/10.1017/S0022215117002249.
7. Mozafari Nia K, Sepehri G, Khatmi H, Shakibaie MR. Isolation and antimicrobial susceptibility of bacteria from chronic suppurative otitis media patients in Kerman, Iran. *Iran Red Crescent Med J*. 2011;**13**(12):891–4. [PubMed ID: 22737435]. [PubMed Central ID: PMC3371905].
8. Bafghi AF, Peyvandi AA, Fathololoomi MR, Nohi SAEIDOLLAH. Pathogens of suppurative chronic otitis media (SCOM) in Iran. *J Med Counc Islam Rep Iran*. 2010;**28**(4):397–462.
9. Zamani S, Mohammadi A, Hajikhani B, Abiri P, Fazeli M, Nasiri MJ, et al. Mupirocin-Resistant Staphylococcus aureus in Iran: A Biofilm Production and Genetic Characteristics. *Biomed Res Int*. 2022;**2022**:7408029. [PubMed ID: 35075429]. [PubMed Central ID: PMC8783719]. https://doi.org/10.1155/2022/7408029.
10. Goudarzi M, Bahramian M, Satarzadeh Tabrizi M, Udo EE, Figueiredo AM, Fazeli M, et al. Genetic diversity of methicillin resistant Staphylococcus aureus strains isolated from burn patients in Iran: ST239-SCCmec III/t037 emerges as the major clone. *Microb Pathog*. 2017;**105**:1–7. [PubMed ID: 28179118]. https://doi.org/10.1016/j.micpath.2017.02.004.
11. Goudarzi M, Kobayashi N, Dadashi M, Pantucek R, Nasiri MJ, Fazeli M, et al. Prevalence, Genetic Diversity, and Temporary Shifts of Inducible Clindamycin Resistance Staphylococcus aureus Clones in Tehran, Iran: A Molecular-Epidemiological Analysis From 2013 to 2018. *Front Microbiol*. 2020;**11**:663. [PubMed ID: 32425898]. [PubMed Central ID: PMC7204094]. https://doi.org/10.3389/fmicb.2020.00663.
12. Goudarzi H, Goudarzi M, Sabzehali F, Fazeli M, Salimi Chirani A. Genetic analysis of methicillin-susceptible Staphylococcus aureus clinical isolates: High prevalence of multidrug-resistant ST239 with strong biofilm-production ability. *J Clin Lab Anal*. 2020;**34**(11). e23494. [PubMed ID: 32696587]. [PubMed Central ID: PMC7676197]. https://doi.org/10.1002/jcla.23494.
13. Castanheira M, Watters AA, Mendes RE, Farrell DJ, Jones RN. Occurrence and molecular characterization of fusidic acid resistance mechanisms among Staphylococcus spp. from European countries (2008). *J Antimicrob Chemother*. 2010;**65**(7):1353–8. [PubMed ID: 20430787]. https://doi.org/10.1093/jac/dkq094.
14. Hajikhani B, Goudarzi M, Kakavandi S, Amini S, Zamani S, van Belkum A, et al. The global prevalence of fusidic acid resistance in clinical isolates of Staphylococcus aureus: a systematic review and meta-analysis. *Antimicrob Resist Infect Control*. 2021;**10**(1):75. [PubMed ID: 33933162]. [PubMed Central ID: PMC8088720]. https://doi.org/10.1186/s13756-021-00943-6.
15. Goudarzi M, Tayebi Z, Dadashi M, Miri M, Amirpour A, Fazeli M. Characteristics of community-acquired methicillin-resistant Staphylococcus aureus associated with wound infections in Tehran, Iran: High prevalence of PVL+ t008 and the emergence of new spa types t657, t5348, and t437 in Iran. *Gene Rep*. 2020;**19**:100603. https://doi.org/10.1016/j.genrep.2020.100603.
16. Rahimi F, Bouzari M, Katouli M, Pourshafie MR. Antibiotic Resistance Pattern of Methicillin Resistant and Methicillin Sensitive Staphylococcus aureus Isolates in Tehran, Iran. *Jundishapur J Microbiol*. 2013;**6**(2):144–9. https://doi.org/10.5812/jjm.4896.

17. Hasani A, Sheikhalizadeh V, Hasani A, Naghili B, Valizadeh V, Nikoonijad AR. Methicillin resistant and susceptible Staphylococcus aureus: Appraising therapeutic approaches in the Northwest of Iran. *Iran J Microbiol*. 2013;**5**(1):56–62. [PubMed ID: 23467268]. [PubMed Central ID: PMC3577566].
18. Chen HJ, Hung WC, Tseng SP, Tsai JC, Hsueh PR, Teng LJ. Fusidic acid resistance determinants in Staphylococcus aureus clinical isolates. *Antimicrob Agents Chemother*. 2010;**54**(12):4985–91. [PubMed ID: 20855746]. [PubMed Central ID: PMC2981276]. https://doi.org/10.1128/AAC.00523-10.
19. den Heijer CD, van Bijnen EM, Paget WJ, Stobberingh EE. Fusidic acid resistance in Staphylococcus aureus nasal carriage strains in nine European countries. *Future Microbiol*. 2014;**9**(6):737–45. [PubMed ID: 25046521]. https://doi.org/10.2217/fmb.14.36.
20. Dadashi M, Hajikhani B, Darban-Sarokhalil D, van Belkum A, Goudarzi M. Mupirocin resistance in Staphylococcus aureus: A systematic review and meta-analysis. *J Glob Antimicrob Resist*. 2020;**20**:238–47. [PubMed ID: 31442624]. https://doi.org/10.1016/j.jgar.2019.07.032.
21. Babu T, Rekasius V, Parada JP, Schreckenberger P, Challapalli M. Mupirocin resistance among methicillin-resistant Staphylococcus aureus-colonized patients at admission to a tertiary care medical center. *J Clin Microbiol*. 2009;**47**(7):2279–80. [PubMed ID: 19474267]. [PubMed Central ID: PMC2708468]. https://doi.org/10.1128/JCM.01834-08.
22. Desroches M, Potier J, Laurent F, Bourrel AS, Doucet-Populaire F, Decousser JW, et al. Prevalence of mupirocin resistance among invasive coagulase-negative staphylococci and methicillin-resistant Staphylococcus aureus (MRSA) in France: emergence of a mupirocin-resistant MRSA clone harbouring mupA. *J Antimicrob Chemother*. 2013;**68**(8):1714–7. [PubMed ID: 23535880]. https://doi.org/10.1093/jac/dkt085.
23. Liu QZ, Wu Q, Zhang YB, Liu MN, Hu FP, Xu XG, et al. Prevalence of clinical meticillin-resistant Staphylococcus aureus (MRSA) with high-level mupirocin resistance in Shanghai and Wenzhou, China. *Int J Antimicrob Agents*. 2010;**35**(2):114–8. [PubMed ID: 19939636]. https://doi.org/10.1016/j.ijantimicag.2009.09.018.
24. Abimanyu N, Murugesan S, Krishnan P. Emergence of methicillin-resistant Staphylococcus aureus ST239 with high-level mupirocin and inducible clindamycin resistance in a tertiary care center in Chennai, South India. *J Clin Microbiol*. 2012;**50**(10):3412–3. [PubMed ID: 22855516]. [PubMed Central ID: PMC3457429]. https://doi.org/10.1128/JCM.01663-12.
25. Boswihi SS, Udo EE, Al-Sweih N. Shifts in the Clonal Distribution of Methicillin-Resistant Staphylococcus aureus in Kuwait Hospitals: 1992-2010. *PLoS One*. 2016;**11**(9). e0162744. [PubMed ID: 27631623]. [PubMed Central ID: PMC5025013]. https://doi.org/10.1371/journal.pone.0162744.
26. Khan AA, Ali A, Tharmalingam N, Mylonakis E, Zahra R. First report of mecC gene in clinical methicillin resistant S. aureus (MRSA) from tertiary care hospital Islamabad, Pakistan. *J Infect Public Health*. 2020;**13**(10):1501–7. [PubMed ID: 32517997]. https://doi.org/10.1016/j.jiph.2020.05.017.
27. Kerschner H, Harrison EM, Hartl R, Holmes MA, Apfalter P. First report of mecC MRSA in human samples from Austria: molecular characteristics and clinical data. *New Microbes New Infect*. 2015;**3**:4–9. [PubMed ID: 25755883]. [PubMed Central ID: PMC4337937]. https://doi.org/10.1016/j.nmni.2014.11.001.
28. Dermota U, Zdovc I, Strumbelj I, Grmek-Kosnik I, Ribic H, Rupnik M, et al. Detection of methicillin-resistant Staphylococcus aureus carrying the mecC gene in human samples in Slovenia. *Epidemiol Infect*. 2015;**143**(5):1105–8. [PubMed ID: 25036113]. [PubMed Central ID: PMC9507135]. https://doi.org/10.1017/S0950268814001861.
29. Basset P, Prod'hom G, Senn L, Greub G, Blanc DS. Very low prevalence of meticillin-resistant Staphylococcus aureus carrying the mecC gene in western Switzerland. *J Hosp Infect*. 2013;**83**(3):257–9. [PubMed ID: 23384824]. https://doi.org/10.1016/j.jhin.2012.12.004.
30. Garcia-Alvarez L, Holden MT, Lindsay H, Webb CR, Brown DF, Curran MD, et al. Meticillin-resistant Staphylococcus aureus with a novel mecA homologue in human and bovine populations in the UK and Denmark: a descriptive study. *Lancet Infect Dis*. 2011;**11**(8):595–603. [PubMed ID: 21641281]. [PubMed Central ID: PMC3829197]. https://doi.org/10.1016/S1473-3099(11)70126-8.
31. Che Hamzah AM, Yeo CC, Puah SM, Chua KH, A. Rahman NI, Abdullah FH, et al. Tigecycline and inducible clindamycin resistance in clinical isolates of methicillin-resistant Staphylococcus aureus from Terengganu, Malaysia. *J Med Microbiol*. 2019;**68**(9):1299–305. [PubMed ID: 31140965]. https://doi.org/10.1099/jmm.0.000993.
32. Zorgani A, Elahmer O, Ziglam H, Ghenghesh KS. In-vitro activity of tigecycline against methicillin-resistant Staphylococcus aureus isolated from wounds of burn patients in Tripoli-Libya. *J Microbiol Infect Dis*. 2012;**2**(3):109–12. https://doi.org/10.5799/ahinjs.02.2012.03.0053.
33. Yousefi M, Fallah F, Arshadi M, Pourmand MR, Hashemi A, Pourmand G. Identification of tigecycline- and vancomycin-resistant Staphylococcus aureus strains among patients with urinary tract infection in Iran. *New Microbes New Infect*. 2017;**19**:8–12. [PubMed ID: 28663797]. [PubMed Central ID: PMC5479968]. https://doi.org/10.1016/j.nmni.2017.05.009.
34. Shariati A, Dadashi M, Chegini Z, van Belkum A, Mirzaii M, Khoramrooz SS, et al. The global prevalence of Daptomycin, Tigecycline, Quinupristin/Dalfopristin, and Linezolid-resistant Staphylococcus aureus and coagulase-negative staphylococci strains: a systematic review and meta-analysis. *Antimicrob Resist Infect Control*. 2020;**9**(1):56. [PubMed ID: 32321574]. [PubMed Central ID: PMC7178749]. https://doi.org/10.1186/s13756-020-00714-9.
35. Dabul AN, Camargo IL. Molecular characterization of methicillin-resistant Staphylococcus aureus resistant to tigecycline and daptomycin isolated in a hospital in Brazil. *Epidemiol Infect*. 2014;**142**(3):479–83. [PubMed ID: 23714160]. [PubMed Central ID: PMC9151117]. https://doi.org/10.1017/S0950268813001325.
36. Jarajreh D, Aqel A, Alzoubi H, Al-Zereini W. Prevalence of inducible clindamycin resistance in methicillin-resistant Staphylococcus aureus: the first study in Jordan. *J Infect Dev Ctries*. 2017;**11**(4):350–4. [PubMed ID: 28459227]. https://doi.org/10.3855/jidc.8316.
37. Adhikari RP, Shrestha S, Barakoti A, Amatya R. Inducible clindamycin and methicillin resistant Staphylococcus aureus in a tertiary care hospital, Kathmandu, Nepal. *BMC Infect Dis*. 2017;**17**(1):483. [PubMed ID: 28693489]. [PubMed Central ID: PMC5504788]. https://doi.org/10.1186/s12879-017-2584-5.
38. Bottega A, Rodrigues Mde A, Carvalho FA, Wagner TF, Leal IA, Santos SO, et al. Evaluation of constitutive and inducible resistance to clindamycin in clinical samples of Staphylococcus aureus from a tertiary hospital. *Rev Soc Bras Med Trop*. 2014;**47**(5):589–92. [PubMed ID: 25467260]. https://doi.org/10.1590/0037-8682-0140-2014.