R.Rajeswari Anburaj et al /J. Pharm. Sci. & Res. Vol. 12(8), 2020, 1018-1023

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Colonization, epidemiology and genetic mechanism of methicillin resistant *Staphylococcus aureus*

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Abstract

Infections caused by *Staphylococcus aureus* strains with Methicillin resistance are associated with increased mortality and morbidity, aggressive course, multiple drug resistance and hospital outbreaks. Life‐threatening infections which were limited only in hospitals are now becoming widespread in community. High usage of antibiotics in hospitals and selection pressure of these antibiotics has been implicated in development of multidrug resistance (MDR) in hospital acquired MRSA. Resistance to methicillin is determined by the mecA gene, which encodes the low-affinity penicillin-binding protein PBP. Current research suggests these natural products have the prospect of being considered for treatment of MRSA infections. The review discuss about the incidence, risk factors and bioactive natural products with anti- MRSA activity.

Keywords*: Antimicrobial resistance, MRSA, mec A, vancomycin, PVL, epidemiology*

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus*(MRSA) was first described in the early 1960s[1]. It is one of the main causes of hospital and community acquired infections, resulting in serious consequences, and the disease ranges from skin infections to septic shock [2]. It is a significant bacterium because it leads to a wide range of diseases such as rashes, inflammations of bones and the meninges as well as septicemia and has a capacity to adapt to different environments. *S.aureus* is now resistant to methicillin via the attainment of an exogenous mobile gene that integrates into its chromosomal DNA[3]. MRSA are widespread in different countries both in hospital environments and take place in community, and livestock MRSA is endemic in hospitals worldwide. In this meta-regression, contact animals, children and working in hospital were risk factors for MRSA carriage [4]. In current days, the incidence of MRSA is rising. The infection due to the MRSA strains has a higher mortality rate than the infection caused by the methicillin- sensitive *Staphylococcus aureus* (MSSA) strains, which brings great difficulty to treatment [5,6]. The term "methicillin-resistant *Staphylococcus aureus*" (MRSA) specifies the variants of *S. aureus* that are resistant to many antibiotics, either in the hospital or a community setting; for example, medications like imipenem, oxacillin, methicillin, cephalosporins, nafcillin, and/or drugs classified as beta-lactamase inhibitors[3]. MRSA can result in disastrous clinical outcomes with high mortality and morbidity rates. In the United States alone, the annual death toll caused by MRSA is estimated to be 20,000 cases[7]. A number of preceding studies have recognized that MRSA resistance to erythromycin and clindamycin, this cross-resistance can be enhanced by erythromycin ribosomal methylase encoding genes[8]. Assessments of the burden of MRSA infections and the need for aggressive infection prevention and control measures focus mainly on infections identified prior to the patient being discharged from the hospital. This review aims to study the prevalence, resistance and molecular mechanism of MRSA infection.

Colonization of MRSA

Asymptomatic colonization is common although it can cause a variety of human and animal infections including fatal courses, as described for *S. aureus* and MRSA where heavily colonized carriers are more likely to be infected than transient or intermittent carriers[9]. Prior reports convey that high clonal diversity was reported among MRSA isolates collected from community members, clinical students and healthcare workers[10]. Elevated risk of colonization mirrors risk of infection as noted above: athletes, those in prisons, military recruits, children, persons in urban, individuals with an indigenous background, pet owners, livestock workers, individuals with prior MRSA infection, individuals with HIV or cystic fibrosis and individuals with frequent health- care contact are all at increased risk of MRSA colonization. For example, reports from India showed nasal MRSA colonization was 3.9% of all nasal staphylococcal strains, where as it was only 1.5% in the United States. In saudi Arabia, among 25% of the people nasal carriage was isolated with *S. aureus* strains[11]. Recent receipt of antibiotics has also been associated with elevated risk of MRSA carriage[12]. Determining exactly how long colonization persists is challenging, though some have observed MRSA persistence greater than six months after initial infection or contact with MRSA[13]. In addition to the nares, MRSA colonization has been detected in oropharyngeal, axillary, perineal, rectal, perirectal and even intestinal samples[14]Targeted decolonization efforts have similarly decreased surgical- site infections in patients receiving cardiac surgery[15] MDR may infect different parts of the body including wounds, respiratory tract, soft tissue, skin and bloodstream particularly in immunocompromised, elderly or young patients[16].

Pathogenesis

Community Associated MRSA can result in severe invasive infections such as septicemia, necrotizing pneumonia and necrotizing fasciitis. Clinical conditions like osteomyelitis, deep-seated abscess, pyomyositis, and invasive CNS involvement in a Saudi tertiary hospital were reported[17]. As stated, investigations on CA-MRSA

in Saudi Arabia are limited. More studies need to be conducted as many international reports have confirmed that CA-MRSA is now more prevalent than HA-MRSA infections. Predisposing factors for CA-MRSA infection include direct contact with CA-infected or colonized individuals, crowded living conditions, poor hygiene, sharing of intimate items and contact physical activities[18]. The infection control implementers in Saudi Arabia to pay more attention to the elderly undergoing HD as they might be more vulnerable for MRSA-linked vascular access-related septicaemia[19]. Diverse clones are dominated in various geographical regions, Only minority of them were affected with HA-MRSA clones are accountable for the greater part of infections The wide spectrum of bone and joint pathologies include infection of prostheses, osteomyelitis, and septic arthritis[20]. Surgery for endocarditis with associated valve dysfunction (particularly if severe enough to cause heart failure), anatomic complication (such as valve perforations, heart block or perivalvular extension) or high risk of embolization. Most recommendations regarding the surgical indications and timing are based on either small observational studies or expert opinion[21]

Vancomycin resistant MRSA

In recent years, hVISA and VISA associated vancomycin treatment failure are becoming an increasing clinical challenge. Several studies have reported the occurrence of vancomycin MIC creep in *S. aureus*[22, 23]. Vancomycin and teicoplanin exhibit antimicrobial activity by binding to D-Ala-D-Ala subunits of the murein monomer. Therefore, cross-resistance can be expected between these antibiotics. The thickening of the cell wall contributes to the development of vancomycin and teicoplanin non-susceptibility in *S. aureus*. A higher vancomycin and teicoplanin MIC of ≥1.5 μg/ml has been linked to poor clinical outcomes in patients with MRSA bacteremia strains[24, 25]. There is a main difficulty in understanding the genetic mechanism of glycopeptide resistance because of the lack of universal resistance markers in hVISA/VISA strains. The genes vraSR, graSR, walKR and rpoB have been frequently associated with the development of heterogeneous resistance to vancomycin[26] In recent years, heterogeneous vancomycin-intermediate *S. aureus* (hVISA) and vancomycin-intermediate *S. aureus* (VISA) have been frequently reported worldwide[27-29]. Elevated levels of vancomycin were expressed in hVISA phenotype. These subpopulations are present at the approximate frequencies of 10^{-4} to 10^{-6}[30]. Studies have suggested that hVISA infections are associated with persistent bacteremia, treatment failure, and poor outcomes [31]. Notably, teicoplanin resistant MRSA (>8 μg/ml) has been documented with a gradual rise in vancomycin MIC (2 to 4 μg/ml) [32]. However, vanA mediating high-level vancomycin resistance in *S. aureus* is rare. CLSI-recommended MIC testing methods, of broth microdilution (BMD) and agar dilution (AD) method are reported to have sub-optimal sensitivity in detecting hVISA and heterogeneous resistance to teicoplanin. These subpopulations mature gradually with several qualities such as sharp, colourless colonies, and alteration in haemolytic pattern [33]. A change in the expression of pbp2 and pbp4 leads to a thickened cell wall in *S. aureus* with reduced vancomycin susceptibility. Upregulation of pbp2 promotes cell wall synthesis, and downregulation of pbp4 results in decreased murein cross-linking. These considerable changes may produce amplified D-Ala-D-Ala subunits which entrap most of the vancomycin molecule. In our study, significant pbp2 upregulation was noted in TR-MRSA (MIC 16 or 32 μg/ml) and four hVISA strains. However, none of the tested isolates showed significant pbp4 downregulation. This could be due to differences in the mutation occurring in co-expressed genes which are involved in cell wall synthesis.

Role of PVL in MRSA

PVL-associated *S. aureus* (PVL-SA) disease is frequently related with community-acquired methicillin resistant *S. aureus* (CAMRSA)[34]. Panton-Valentine leukocidin (PVL, composed of *LukS-PV* and *LukF-PV*), a pore-forming toxin causing leukocytolysis and tissue necrosis, is one of these virulence factors that may have a significant influence in some serious *Staphylococcus aureus* (*S. aureus*) infections, such as severe skin and soft tissue infection, necrotizing pneumonia, and necrotizing fasciitis[35,36]. Molecular modeling indicates that a single amino acid replacement at site 176 [histidine (His) to arginine (Arg), namely H isoform changing into R isoform] may increase the leukotoxicity of PVL[37]. *S. aureus* is currently the most prevalent pathogen causing bacteraemia (Darboe et al., 2019)[38] The prevalence of PVL (72.9%) in invasive disease was unusually high but similar to that found in Ghana (75%) and greater than reported in the neighboring country of Senegal (47%), elsewhere in Africa and across the globe. Antibiotic susceptibility was alike for *S. aureus* causing infection in other parts Africa where multidrug resistance continues to be high for penicillin, sulfamethoxazole-trimethoprim and tetracycline[39]. Genestier *et al*.[40] reported that the role of PVL depends on the amount of toxin generated by *S. aureus*. In previous reports, the mean value and median of PVL production of SSTI isolates were relatively high compared with those of isolates from pneumonia, surgical site infections, and other infections. The number of *S. aureus* isolates producing PVL is mainly determined using polymerase chain reaction (PCR) for *lukSF-PV* genes or quantitative reverse transcription–PCR for *lukSF-PV* mRNA levels Chuanling Zhang, 2018[41]. Moreover, the only existence of a virulence gene does not imply that the toxin will be transcribed and/or translated and, if it is transcribed and/or translated, the toxin yield can be significantly different among isolates[42]. Preceding reports showed that the *lukSF-PV* genes were a frequent genetic marker of CA MRSA isolates with SCC*mec*IV or SCC*mec*V [43,44].

Genetics and Molecular mechanism

MRSA resistance to betalactam antibiotics is due to the acquisition of *mec* genes within a mobile genetic cassette (SCC*mec*) in the staphylococcal chromosomal DNA,

leading to altered penicillin-binding proteins[45,46]. Types of mec gene complex and genotypic methods were characterized in Table:1 & 2. Genetically, SCC*mec* is classified into eight different genotypes (I-VIII) with some divided further into subtype[47]. MRSA identification method was based on mec A gene among them. Some were cefoxitime disk diffusion method[48]. They collected 103 swab samples and concluded that the majority of the MRSA isolates belonged to SCC*mec* types V and IVa and were included in four clonal complexes, CC5, CC8, CC22, and CC80 [49].The homologue was most recently identified and was reported in March 2017 from an *M. caseolyticus* strain isolated from bovine and canine sources; it shows about 61% nucleotide sequence identity to the original *mecA* gene[50]. A new *mec* variant, named *mecC*, which shows only 70% nucleotide sequence homology with the classical *mecA* gene was described in 2011. Resistance to cefoxitin was reported as correctly identifying *mecC*-positive MRSA[51]. In previous study 9 strains of 117 isolates were ST239 MRSA-III whereas all others were of CA- MRSA lineages as they harboured SCC*mec* IV and V[52]. The use of targeted DNA microarrays represents another technique to detect genes associated with SCC*mec*, including *mecA*, its regulatory elements, various allotypes, and J regions, and consequently can be used for the identification of known SCC*mec* types[53]. Regarding MRSA strains, the New York/Japan (ST5/SCC*mec* II) and Brazilian/Hungarian (ST239/SCC*mec* III) clones are widespread globally and connected to HA-MRSA isolates while the Taiwanese (ST59/SCC*mec* IV or V), USA300 (ST8/SCC*mec* IV), European (ST80/ SCC*mec* IV), and USA400 (ST1) clones are always connected to CA-MRSA.[54] Recently Baig et al. (190) isolated a new type of SCC*mec* type XIII in MRSA ST152. The element is 32.3 kb in length and harbors a novel *ccrC2* gene. The structure of its *mec* gene complex, however, resembles that of the *mec* class A complex (*mecI-mecR1-mecA*-IS*431*) with an additional IS*431* downstream of *mecI*. Additionally, the order of the genes in the *mec* gene complex of SCC*mec* type XIII is inverted compared to that of the prototype class A *mec* gene complex. Moreover, it contains a gentamicin resistance gene on a transposon, Tn*4001*, found in the J2 region of the element[55].

Table:1 Five types of mec gene complex

SCC mec Type	Size(kb)	Features
I	34.3	Lacks other resistance genes
II	53.0	linked with multiple drug resistance
III	66.9	connected with multiple drug resistance
IV	20.9-24.3	Resistance to β-lactam antibiotics
V	28.0	antibiotic resistance genes are absent except mec A

SCC= staphylococcal cassette syndrome

Table: 2 Genotypic methods in MRSA typing

S.no	Methods	Principle
1.	Multilocus VNTR analysis	Polymorphism is expressed
2.	Pulse field gel electrophoresis	*S. aureus* DNA fragments are produced with exclusive band patterns that are then compared with those of additional isolates to classify associated strains
3.	Rep- PCR typing	Polymorphismis expressed in chromosomal inter-repeat element spacers
4.	*S. aureus* protein A (spa)	polymorphic region X includes mutation in the variable repeats of 24bp
5.	SCC*mec* typing	7 major *mec* and ccr gene of 7 major SCC*mec* types

Epidemiology

In the United States, MRSA causes between 11,000 and 18,000 deaths annually and 80,000 invasive infections[56,57]. The random use of antimicrobial agents in animal husbandry and other agricultural actions has chiefly contributed to the extensive distribution of MRSA amongst livestock. It has affected more than 40% of pigs, 20% of cattle, and 20 to 90% of turkey farms in Germany[58]. The incidence of MRSA in Saudi Arabia varies considerably from region to region. Bush and coworkers (487) recently (April 2011 to March 2013) conducted a complete provincial surveillance of all acute-care facilities in Alberta, Canada, and reported the predominance of CMRSA2/USA100. That study reported that the USA300 clone replaced the NewYork/Japan clone as the most dominant type causing nosocomial infections in the New York metropolitan area[59]. The rate of MRSA prevalence in the Western, Central, and Eastern regions is 42%, 32%, 27%, respectively. [60,61]. In Europe and North America, CC398 is the most dominant LA-MRSA strain, although it has also been detected sporadically in Asia and Africa[62,63] Bouchiat et al. found that 54.8% of the total *S. aureus* isolates among samples from a hospital in eastern Uttar Pradesh were methicillin resistant. Previous studies concluded that the USA300 clone replaced the NewYork/Japan clone as the most dominant type causing nosocomial infections in the New York metropolitan area[64]. Further, 57.3% of the blood cultures from a Neonatal Intensive Care Unit in Amritsar were methicillin resistant [65]. The ST22 strain appears to be gradually overtaking ST239, another widely distributed HA- MRSA strain (from CC8) that has been found in Europe, the Middle East, Asia and the Pacific[66].

Treatment

Medicinal plants with anti-MRSA potentials were described in Table: 3. Quinoline is a versatile heterocyclic moiety having diverse spectrum of biological activities including anti-Alzheimer's, anticancer [67], anticonvulsant, antidiabetic [68], antihypertensive, anti-inflammatory[69], antimicrobial [70] and ubiquitination inhibition [71] Zheng et al. carried out antibacterial evaluation of a series of benzofuroquinolinium derivatives

as FtsZ polymerization inhibitors which inhibits cell division and causes cell death. All the five compounds were tested against a panel of bacterial strains including resistant strains. Among the tested compounds, 2 was most potent anti-MRSA agent having MIC values 1, 1, 1, 1 and 0.5 μg/ mL against MRSA strains ATCC 43300, BAA-41, 33591, BAA-1720 and 33592 respectively and exerted its effect by inhibiting cell-division protein FtsZ [72]. Teng et al. synthesized a series of quinoline derivatives as antibacterial agents. The synthesized compounds were tested for their antibacterial activity against resistant bacterial strains viz. MRSA, MRSE and VRE. Antibacterial activity results indicated that compound **3** was most potent anti-MRSA agent having MIC value 1.5 μg/mL [73]. The level of resistance to fluoroquinolones, clindamycin and erythromycin of our MRSA isolates was similar to the resistance level of MRSA isolates in Italy, while percentages of isolates resistant to gentamicin and tetracycline in Italy [74] was slightly higher than in previous research. The optimal duration of treatment remains controversial, though in the specific case of MRSA vertebral osteomyelitis, durations less than 8 weeks may be associated with increased risk of recurrence[75]. Incision and drainage should be performed whenever possible for purulent ABSSSIs. A recent large, placebo- controlled trial confirmed that antibiotic therapy reduces the likelihood of recurrent abscesses or treatment failure following incision and drainage[76]. Delafloxacin and omadacycline, were the two antimicrobials used as trials in MRSA(Debio 1450)[77]. Two long half- life, single- dose injectable agents, oritavancin and dalbavancin, have also proved non- inferior to vancomycin[78].V710, a monovalent vaccine targeting iron salvage protein IsdB, was actually associated with increased mortality, resulting in early termination of the trial[79]. In particular, SDG3 (Ensure healthy lives and promote well-being for all at all ages) is severely impacted by AMR(antimicrobial resistance), as several of the adopted targets in this health-dedicated SDG(sustainable development goals) will be impossible to achieve without the availability of effective antibiotics[80].

Table: 3 Medicinal plants with anti-MRSA properties

S.no	Plant	Active phytochemicals
1.	*Hemidesmus indicus*	hemidine, hemidescine, emidine
2.	*Plumbago zeylanica*	plumbagin
3.	*Delonix regia*	Zeaxanthin
4.	*Punica granatum*	Punicalagin and ellagic acid
5.	*Emblica officinalis*	Zeatin nucleotide and zeatinriboside
6.	*Acorus valamus*	α and β‑asarone
7.	*Camellia sinensis*	Caeffine, flavonoids, kaempferol

CONCLUSION

Methicillin-resistant *S. aureus* have evolved appreciably over the previous years with vital medical and epidemiological implications. Use of antibiotics in animal and human therapeutics and in animal agriculture has resulted in the emergence and spread of multidrug resistance in many pathogens. The key factors contributing to the concentrated incidence of MRSA, as well as host and ecological factors related with its decline could aid in managing the future outbreaks of MRSA.

Conflict of interest

The authors declare that there is no conflict of interest.

Acknowledgement

The authors would like to extend their sincere gratitude to Dhanalakshmi Srinivasan College of Arts and Science for the facilities provided.

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