Chapter 1

The Evolution and Dissemination of Methicillin Resistance Determinant in *Staphylococcus aureus*

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Abstract

Staphylococcus aureus is an opportunistic pathogen and is frequently associated with the antimicrobial resistance. There has been horizontal gene transfer of *Staphylococcus* chromosome cassette *mec* (SCC*mec*) among the staphylococcal species that colonize a similar colonization niche, which eventually results in emergence of new variant with enhanced survival ability in terms of antimicrobial resistance and virulence level in *S. aureus*. Evolution and dissemination of SCC*mec* structure resulted in the emergence of methicillin-resistant *S. aureus* (MRSA) clones around the world covering hospital, community, and livestock settings. MRSA also has the ability to resist different antibiotic profiles known as multidrug-resistant *S. aureus* (MDR *S. aureus*).

Keywords: *Staphylococcus aureus*, SCC*mec*, MRSA clones, multi-drug-resistant *S. aureus*

1. Introduction

Staphylococcus aureus is an opportunistic pathogen and lives as part of the animal normal flora of skin and nasopharynx. Favorably, it resides in the nasal mucosal environment posing infection threat to human as well as in domestic animals [1, 2]. In human, it is the leading agent of infection involving bloodstream, skin, and soft tissue to the lower respiratory tract [3–5]. *S. aureus* can easily colonize certain part of the body, especially the exposed area on skin due to ulcers, burns, and surgical wounds [6].

Methicillin-resistant *S. aureus* (MRSA) has been well known for being resistant to β-lactam antibiotics, which are the most common antimicrobial agents used to fight staphylococcal infection. Previous studies reported that methicillin resistance in staphylococci was carried by a specific mobile genetic element (MGE) called staphylococcal chromosome cassette *mec* (SCC*mec*), which carries with it several virulence factors as well [7]. SCC*mec* contains *mecA* gene which encodes for a low affinity penicillin-binding protein (pbp2a or pbp2′), which is currently exploited as the methicillin resistance marker in Staphylococcus species including *S. aureus* [8]. SCC*mec* contains several elements that can be categorized into several types. Genetic events such as point mutation, recombination, acquisition, and deletion, coupled with host and environmental selective pressures, make the structure evolve and disseminate in the population [9]. The emergence of certain MRSA clones, which have been disseminating worldwide since 1960, was closely related to the continuous evolution of SCC*mec* structure in *S. aureus*.

Multidrug-resistant MRSAs have also been reported that make the antibiotic regiment limited. Prevalence of MRSA is of a growing concern, particularly due to the more recent increased frequency of community-associated MRSA (CA-MRSA) and livestock-associated MRSA (LA-MRSA). Thus, this pathogen becomes a major concern in public health as well as livestock industry [10–13].

Many studies have been looking at the mechanism and dissemination pattern of MRSA and its genetic characteristics, but due to the potential, geographical, and temporal differences, a comprehensive review is needed to put the whole picture connected.

2. *Staphylococcus aureus*

S. aureus is a Gram-positive bacterium with a grape-like cluster morphology and can usually be found in skin or mucous membrane, especially in nasal of healthy person [14]. Kluytmans et al. reported that approximately 20–30% of human population carries *S. aureus* [15]. Morphologically, *S. aureus* can be observed as a 'golden' medium-size colony on solid media such as nutrient agar and can cause β-hemolysis on sheep blood agar [16].

The production of golden pigmentation of *S. aureus* colonies is closely related to the presence of carotenoids which is previously reported as virulence factor protecting *S. aureus* from the immune system [17]. Among Staphylococcus species, only *S. aureus* has the ability to ferment mannitol leading to the production of lactic acid on mannitol salt agar with yellow zones around the colonies [18]. *S. aureus* is also classified as a halophilic bacterium for being able to live in the presence of salt (sodium chloride) up to 1.7 molar. It also produces coagulase that causes blood to clot [14].

Generally, 20–30% of individuals are persistent carriers of *S. aureus* and 30% are transient or intermittent carriers [19]. *S. aureus* may live in human without any clinical symptoms, but it may infect the host when the host defense system is compromised. Individuals may acquire infection by *S. aureus* that they previously carry as commensal [15].

Immunocompromised patients with *S. aureus* infection may suffer several diseases such as bacteremia, ventilator-assisted pneumonia (VAP), endocarditis, and osteomyelitis, especially when the patients are frequently exposed to injections and catheter insertions [20, 21]. *S. aureus* can also cause toxin-mediated disease such as toxic shock syndrome, scalded skin syndrome, and Staphylococcal foodborne diseases (SFD) [21]. Frequently, *S. aureus* is the main cause of skin and soft tissue infection (SSTI) in human [22].

3. Methicillin-resistant *S. aureus* (MRSA)

MRSA has the ability to resist almost all available β-lactam antibiotics. Statistics showed about 40–70% of *S. aureus* nosocomial infections worldwide are caused by MRSA. MRSA was first reported in a hospital in the United Kingdom in 1961 after the introduction of methicillin to treat patient with penicillin-resistant Staphylococcus infection [23].

Generally, MRSA can be categorized into two major groups known as hospital-associated MRSA (HA-MRSA) and community-associated MRSA (CA-MRSA). Globally, the majority of MRSA infections are HA-MRSA that are acquired from healthcare facilities. Currently, MRSA isolates are subdivided into three major groups known as hospital-associated MRSA (HA-MRSA), community-associated MRSA (CA-MRSA), and livestock-associated MRSA (LA-MRSA). Previous reports revealed that both HA-MRSA and CA-MRSA isolates differ distinctly from each other, with HA-MRSA showing high antimicrobial resistance but less virulence and lack of capabilities as colonizers [23–26]. Meanwhile, CA-MRSA isolates exhibit a low antimicrobial resistance but a high virulence harboring PVL gene and numerous pathogenicity factors, as well as good colonizers [26–29].

MRSA spread in population since 1990 and become the major cause of community-associated infection [27]. The scenario worsens when multidrug MRSA emerges, in which it can resist more than two antibiotics of different classes that reduce the option for available treatment of Staphylococcal infection [30, 31].

Methicillin resistance characteristic in *S. aureus* is due to the presence of altered penicillin-binding protein (PBP2a) in the cell wall that has a reduced binding affinity to β-lactam antibiotics. PBP2a is encoded by *mecA* gene that is located in the large chromosomal cassette called staphylococcal chromosome cassette *mec* element (SCC*mec*) [32–35]. The *mecA* gene expression is controlled by *mecI-mecRI* regulatory genes encoding repressor and inducer protein, respectively [36].

4. SCC*mec* structure

Staphylococcal cassette chromosome *mec* (SCC*mec*) has a size of about 20–60 kb. The structure is unique as it carries various mobile genetic elements that are integrated in it [37]. To date, more than 80 SCC*mec* elements have been identified in several staphylococci species [38].

SCC*mec* disseminates among Staphylococcal species by horizontal gene transfer and integrates at a specific site called *att*B or ISS (integration site sequence) at the 3′ end of *orf*X gene that encodes for unknown function [39].

A single SCC*mec* carries *mec* complex and cassette chromosome recombinase (*ccr*) flanked by direct inverted repeat (DR) and inverted repeat (IR) sequences; *mec* complex consists of *mecA* gene (methicillin resistance determinant), *mecRI* (sensor inducer), and *mecI* (*mec* repressor). Both *mecRI* and *mecI* are recognized as *mec* regulator elements, while *ccr* genes encode serine recombinases (*ccr*A, *ccr*B, *ccr*C) responsible for site and orientation of specific integration and excision of SCC*mec*. In addition, SCC*mec* also harbors other elements such as insertion sequences (IS), plasmids, and transposons [24, 40, 41].

4.1. Complete SCC*mec*

To date, the International Working Group-SCC*mec* (IWG-SCC*mec*) identified eleven SCC*mec* types based on complete nucleotide sequences in Staphylococcal databases, and each SCC*mec* type is named using a roman numeral based on the unique combination of *ccr* complex and *mec* complex [40–42]. A complete SCC*mec* structure in *S. aureus* contains a *mec* complex (*mecA, mecRI* and *mecI*), a *ccr* complex (*ccrA, ccrB, ccrC*), and a J region (region other than *mec* and *ccr* complexes) [40].

Furthermore, many different SCC*mec* subtypes have also been described containing the same *ccr* and *mec* gene combination but vary in the J regions [40]. Among the eleven SCC*mec* types (I–XI) that have been reported so far, five of them (SCC*mec* I, II, III IV, and V) are globally distributed, while others only distributed in certain countries [38, 43]. Three (SCC*mec* IVa, SCC*mec* IVc, SCC*mec* V) from the 11 SCC*mec* types have been detected in MRSA isolated from animals called LA-MRSA [42]. In general, SCC*mec* type IV and V are more widely found among CA-MRSA, and the other three types (SCC*mec* I, II, III) are frequently found among HA-MRSA [44, 45, 46]. An early study by Ito et al. detected only three types of SCC*mec* structures (SCC*mec* type I, II, III) isolated from human [37], and a recent finding showed that MRSA with SCC*mec* type I, II, III is originated from animals [41].

Different types of SCC*mec* in MRSA are also observed to be geographically distributed. For example, SCC*mec* type III or IIIA was most commonly found in Asian countries, but Korea and Japan had more type II while Taiwan had more type IV [47]. SCC*mec* type IV was also commonly found in Latin and European countries [48, 49]. Similarly, in African countries, SCC*mec* type III was also predominant with SCC*mec* types II, IV, and V found in selected countries such as Egypt, Niger, Nigeria, Algeria, Tunisia, and South Africa [50].

4.2. Pseudo-SCC*mec*

Pseudo-SCC*mec* is recognized as SCC*mec* that does not carry *ccr* complexes but has *mecA* gene. Although this element is different from the complete SCC*mec* in terms of gene or operon organization, it still has some similarities in certain parts in both pseudo-SCC*mec* and complete SCC*mec* structure. Deletion is the major event as inferred by the absence of certain genes or operon in pseudo-SCC*mec* structure. For example, regions within *mec* complex and J region

are absent in both pseudo-SCC*mec* II.5 and pseudo-SCC*mec*16691. It was observed that pseudo-SCC*mec*16691 lacks J1, J2 regions, and *ccr* genes, whereas missing parts were detected in pseudo-SCC*mec* II.5 and replaced by transposable elements called *Tn6012* [51, 52].

However, certain pseudo-SCC*mec* does not carry both *mec* and *ccr* complexes. An example is the arginine catabolic mobile element (ACME) for having SCC-like elements but lack in *mecA* and *ccr* genes. This could be the remnant of SCC*mec* structure that had gone through multiple mutational events. Lindqvist et al. discovered first remnant of pseudo-SCC*mec* structure in methicillin susceptible *S. aureus* (MSSA) that caused clonal outbreak in Sweden. They suggested that this pseudo-SCC*mec* structure could be derived from SCC*mec* type II [52].

ACME is found in both MRSA and MSSA, especially with sequence type ST8 (ST8), and has been disseminated in virulent *S. aureus* by horizontal gene transfer [3, 53]. Nevertheless, ACME was frequently associated with MRSA-IVa with sequence type 8 (ST8-MRSA-IVa), which was also known as CA-MRSA USA300 [3, 53]. ACME has been associated with the ability of CA-MRSA to colonize on other parts of human body such as skin and mucosal membranes rather than limited to only nostril. The acquisition of ACME may enhance the ability of CA-MRSA to survive in acidic environment of human skin by driving production of polyamine-resistant enzyme that combats excess host polyamine (toxic compound on human skin for *S. aureus*) [54].

5. Origin of SCC*mec* structure

The origin of SCC*mec* in MRSA is still in debate; *mecA* gene was believed to be originated from *Staphylococcus fleurettii* due to a high sequence similarity (>99%) with *mecA* gene of a MRSA strain N315. It was proposed that SCC*mec* is a combination of SCC elements without *mec* complex, and the *mec* gene complex was derived from *S. fleurettii* since no evidence showed that *S. fleurettii* contained SCC*mec* structure in its chromosome [55].

Several studies described coagulase-negative staphylococci (CoNS) as the primary reservoir of the SCC*mec* structure in *S. aureus*, which was considered as the recipient strain due to some reasons; a very similar SCC*mec* structure and organization was observed in both *S. aureus* and CoNS [56, 57], and the prevalence of methicillin-resistant coagulase-negative staphylococci (MRCoNS) in human is higher as compared to MRSA [35, 56–59]. Although a study discovered other non-staphylococci species called *Macrococcus* to also carry SCC*mec*-like elements, those were different with SCC*mec* in MRSA in terms of nucleotide sequences and genetic organization of the *mec* complex [55].

5.1. From coagulase-negative staphylococci species to MRSA

The existence of various forms of SCC*mec* in MRCoNS as compared to MRSA becomes the main argument why MRCoNS is suggested as the main reservoir of SCC*mec* for *S. aureus* leading to the emergence of MRSA [40, 57]. In a rapid genetic typing, polymerase chain reaction (PCR) technique is used to characterize the SCC*mec* types instead of nucleotide sequencing

analysis. Consequently, SCC*mec* from MRCoNS is frequently defined as non-typeable due to a diverse combination of *ccr* and *mec* complexes that could not be assigned based on current SCC*mec* structure databases used against *S. aureus* [7]. Nevertheless, Zong et al. successfully assigned 10 SCC*mec* elements with a new combination of *ccr* and *mec* complexes in various species of MRCoNS. They assigned these untypeable SCC*mec* elements as UT1–UT10 [35]. In addition, another study also described new SCC*mec* types in *Staphylococcus hominis* and described those as NT1till NT4 [60].

Staphylococcus epidermidis, *Staphylococcus haemolyticus*, and *S. hominis* were found to carry a diverse SCC*mec* structure among CoNS. SCC*mec* type IV is the common structure found in *S. epidermidis*, while other SCC*mec* types I, II, III, V, VI and non-typeable SCC*mec* were also detected at a lower rate [61, 62]. For *S. haemolyticus*, SCC*mec* type V predominated in combination with other novel SCC*mec* types [60, 63]. In *S. hominis*, SCC*mec* types contained a combination of novel non-typeable SCC*mec*, SCC*mec* types VI, VIII, III, and other elements [35, 61].

5.2. From MSSA to MRSA

MRSA emerges when MSSA receives SCC*mec* structure elements from other MRSA or MRCoNS via horizontal gene transfer [64]. In a specific condition (high vancomycin concentration), SCC*mec* is unstable in certain MRSA that can lead to complete or partial deletion of SCC*mec* structure, which may result in the presence of certain SCC*mec* DNA fragment to remain in *S. aureus* chromosome [64–67].

Wong et al. [64] identified SCC*mec* type II with internal deletion in MSSA isolates from different geographical areas. This happened during *in vitro* exposure to vancomycin [64]. Furthermore, Vandendriessche et al. [67] described MSSA CC398 as the precursor for emergence of MRSA CC398 in livestock. They found non-SCC*mec* elements in MSSA CC398 harboring *czrC* and *tet*(K) genes generated during partial excision of SCC*mec* elements [67].

6. Clonal dissemination of MRSA

Nowadays, the dissemination of MRSA has become a major global problem that threatens human health [27]. However, only limited clones of MRSAs could be inferred to disseminate in different countries and continents through genotypic analysis using several DNA typing methods such as SCC*mec* typing, PFGE, MLST, and spa typing [27, 68, 69]. For example, more than 3000 MRSA isolates from certain continents (Europe, USA, and South America) were described to belong to only five major pandemic clones or clonal complexes (CC5, CC8, CC22, CC30, and CC45) [70]. To date, 11 clonal complexes (CC1, CC5, CC8, CC12, CC15, CC22, CC25, CC30, CC45, CC51, and CC121) have been detected in which 5 of them (CC8, CC15, CC22, CC30, and CC45) were isolated from human [71, 72]. These successful clones may transmit their genetic elements into other *S. aureus*, which are well adapted to hospital environment [73].

MRSA strain COL was the first MRSA clone detected carrying SCC*mec* type I with sequence type 250 (ST 250) and belonged to clonal complex 8 (CC8). Then, other MRSA clones with SCC*mec* type II and III were reported and recognized as EMRSA-1 (ST239), EMRSA-5 (ST247), and New York/Japan clone (ST5, USA100) [74]. Certain MRSA clones were originated from community setting. For example, Wang and co-workers (2007) detected the spread of community-associated SCC*mec* type IV and V MRSA in hospital setting in Taiwan between 1999 and 2005. They concluded that SCC*mec* types IV and V are carried by both CA-MRSA and HA-MRSA [75–77].

The popular human MRSA pandemic clones, the EMRSA-15 and EMRSA-16, were identified in the United Kingdom (UK) around early 1990s. Since then, the clones become predominant healthcare-associated MRSA in UK [78, 79] and several European countries such as Denmark [80], Sweden [81], Belgium [79], and Spain [82]. Studies in Kuwait [83] and USA [84] also reported the spread of EMRSA-15 and 16 clones in hospital setting in the countries. To date, these clones have already been widespread in 15 countries around the world [85]. Both MRSAs belong to SCC*mec* type IV with sequence type 22 (ST 22) for EMRSA-15 and sequence type 30 (ST 30) for EMRSA-16 and originated from hospital setting. EMRSA-15 and 16 have high surviving and spreading rate in hospital compared to other EMRSA in UK [78]. In 2013, MRSA clone with a rare sequence type, ST 779, was identified in eleven Irish hospitals from 2006 until 2011 harboring a novel pseudo (SCC*mec*)-SCC-SCC_{CRISPR} composite element. This clone contained novel *mec* class region, a fusidic acid resistance gene (*fus*C), and two copper resistance genes (*copB* and *copC*) but lacking *ccr* genes [86].

CA-MRSA clones have also been observed to disseminate worldwide particularly with sequence types ST80 and ST30. MRSA clone with ST80 is the most common CA-MRSA clone in European countries and usually carries PVL genes. Moreover, ST80 clone also showed resistance toward fluoroquinolones, tetracyclines, and fusidic acid [87]. CA-MRSA clone with sequence type ST30 was observed to disseminate in Asian and Oceanic countries. An example is the multidrug USA300 clone, known as West Pacific clone. It was first identified in the USA and carried plasmid that encodes several antibiotic resistance genes [88]. Enany et al. identified novel clones with sequence types ST1010 (121)c and ST1009 (1153)c isolated from Egypt after they analyzed different genetic patterns of PVL+CA-MRSA isolates from different countries [89].

In certain countries, it was found that MRSA can also spread among livestock, known as LA-MRSA. LA-MRSA CC398 is the popular clonal complex among livestock and has already been reported to spread in several European farms in Netherland, Denmark, Germany, France, and Italy [90]. MRSA CC398 was originated from pigs and spread among dairy cattle and turkey [91, 92]. In Netherlands, MRSA contamination on meat was reported after 2217 meat samples were analyzed covering 35.3% turkey, 15.2% beef, 15.2% veal, 10.7% pork, and 6.2% lamb meat [93]. LA-MRSA can be transmitted to human by physical contact with livestock contaminated with MRSA [94]. LA-MRSA may have equal virulence ability as compared to CA-MRSA and HA-MRSA toward human. Therefore, persons with continuous exposure to livestock carrying LA-MRSA are at high risk [95]. Other than meat, LA-MRSA can also be found in dairy milk. Recently, 11 sequence types were detected from LA-MRSA isolated from 15 Brazilian dairy

farms (n = 552) with four of them contain novel sequence types (ST1622, ST1623, ST1624, and ST1625) [96].

7. Multidrug-resistant (MDR) MRSA

Antibiotic or antimicrobial drugs are the most effective therapeutic agents used in treating microbial infections through either one or both bactericidal and bacteriostatic effects. Nevertheless, antibiotic or antimicrobial drug resistance has been a major problem worldwide, with incidence of MRSA reported in healthcare facilities in Asia to reach its peak in late 1990s, and stayed at plateau level during 2000s [97]. The heavy usage of drugs in treatment hastens the selection of bacteria that harbor multidrug resistance genes particularly *S. aureus* to proliferate and dominate [98, 99]. Moreover, over-crowded community creates environment that is suitable for the rapid spread of numerous multidrug-resistant pathogens, particularly the airborne organisms such as *S. aureus*.

The emergence of multidrug-resistant *S. aureus* in both hospitals and community invokes a tremendous financial burden due to the persistence of hard-to-treat infections [97, 100–102]. Until present, it was reported that <90% of *S. aureus* strains are resistant to penicillin as well as ordinary antimicrobial agents such as drug from categories of aminoglycosides, ansamycins, anti-staphylococcal β-lactams (or cephamycins), chloramphenicols, fusidanases, fluoroquinolones, glycopeptides, lincosamides, macrolides, phenicols, and tetracyclines [103–105]. We are now observing the emergence of multidrug-resistant *S. aureus* and MDR-MRSA with broad spectrum of resistance with a distinct ability to survive and spread in the hospital environment, community setting, as well as livestock sectors.

There has been a dramatic increase in the incidence of nosocomial infections as well as community-associated MRSA and livestock-associated MRSA caused by strains of *S. aureus* that are resistant to multiple antibiotics [106]. At present, there have been reports that some strains demonstrate resistance to as many as 20 antimicrobial compound types, including antiseptics and disinfectants [107, 108]. Central Asian surveillance studies found that the prevalence of MRSA infection in tertiary hospital was reported in 10 among 1000 hospital admissions [109] and incidence reported previously in Japan was between 0.7 and 0.8 per 100 admission from 1999 to 2003 with a total rate among hospitalized patients in the Asia-Pacific region at 45.9% [110, 111]. Previous surveillance also reported that Asia is among the highest for the incidence of MRSA in the world, and interestingly a novel MRSA strain with glycopeptides resistance had spread in livestock animals making it as a potential human pathogen in this region [112].

Several studies attempted to profile all possible multidrug-resistant MRSA since 1987, encompassing samples from hospitals, community, as well as veterinary settings [113, 114]. Lim et al. (2013) carried out temporal comparative surveillance of antibiograms from clinical samples in 2003–2008 and showed a significant increase in resistance rates (from 1 to 96%), as well as multidrug-resistant phenotypes (96%). This study also indicated the prevalence of multidrug-resistant MRSA with SCC*mec* type III and ST239 [99]. Another study also reported

the prevalence of resistance against other important antibiotics such as mupirocin, whose resistance rate in Malaysia is still low, but still higher than previous reports in Malaysia [107]. Another cross-sectional studies at a few major medical centers in Malaysia found that the occurrence of MRSA infection increased gradually with years, from 25.7 to 28.7% in 1996, 27.9% in 1998, and 33% in 2000 [115, 117, 118]. Meanwhile, a study done at a single Malaysian hospital found a gradual reduction in MRSA prevalence from 2002 to 2006, most likely due to the improvement in the quality of healthcare systems [103, 109, 116 118].

The first international surveillance study on epidemiology of CA-MRSA in Asian countries revealed important findings with regard to the current epidemiology of MRSA infections in the community and hospitals within Asia with multidrug-resistance rates at 73.1 and 83.7% for CA-MRSA and HA-MRSA, respectively [119]. At least, 357 isolates of CA-MRSA were analyzed with resistance rates of gentamicin, ciprofloxacin, and trimethoprim/sulfamethoxazole being significantly lower than those of HA-MRSA isolates, whereas resistance rates of clindamycin, erythromycin, and tetracycline were similarly high in both CA-MRSA and HA-MRSA [119, 120].

8. Conclusion

S. aureus and MRSA evolve and adapt the changing environment. Therefore, dissemination of MRSA should be continuously monitored for the antibiotic susceptibility pattern and molecular epidemiology comprising hospital, community, and livestock settings. The origin and dissemination of SCC*mec* are also important to be tracked in the diverse staphylococcal population. With the advancement in molecular methods such as next-generation sequencing, the pattern of the genetic evolution, spread of the bacteria, and the resistance determinants can be further explored and understood.

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