A Review of Staphylococcal Cassette Chromosome *mec* (SCC*mec*) Types in Coagulase-Negative Staphylococci (CoNS) Species

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Abstract

Coagulase-negative staphylococci (CoNS) are considered low pathogenic organisms. However, they are progressively causing more serious infections with time because they have adapted well to various antibiotics owing to their ability to form biofilms. Few studies have been conducted on CoNS in both, hospital and community-acquired settings, especially in Malaysia. Thus, it is important to study their species and gene distributions. A mobile genetic element, staphylococcal cassette chromosome *mec* (SCC*mec*), plays an important role in staphylococci pathogenesis. Among CoNS, SCC*mec* has been studied less frequently than *Staphylococcus aureus* (coagulase-positive staphylococci). A recent study (8) conducted in Malaysia successfully detected SCC*mec* type I to VIII as well as several new combination patterns in CoNS species, particularly *Staphylococcus epidermidis*. However, data are still limited, and further research is warranted. This paper provides a review on SCC*mec* types among CoNS species.

Keywords: CoNS, epidemiology, SCCmec types, mecA gene

Introduction

Coagulase-negative staphylococci (CoNS) are catalase-positive gram-positive bacteria that do not possess the ability to clot blood plasma. Categorised under the *Micrococcaceae* family, CoNS were believed to be less virulent than *Staphylococcus aureus* (1). However, CoNS have been recently established as one of the major nosocomial pathogens, with *Staphylococcus epidermidis* and *Staphylococcus haemolyticus* being identified as the most significant species (2). John et al. (1) stated that CoNS are the most frequent contaminants of blood cultures owing to their normal habitat on the skin. They may also colonise specific areas and cause particular infections; *Staphylococcus saprophyticus* is responsible for up to 10% of uncomplicated urinary tract infections in young women; *Staphylococcus schleiferi, Staphylococcus lugdunensis,* and *S. haemolyticus* are involved in native valve endocarditis. Newly discovered species such as *Staphylococcus pettenkoferi* and *Staphylococcus nepalensis* can also cause human infections; however, this percentage is lower (1). CoNS can produce biofilms; this makes them more resistant to several antibiotics and thereby more difficult to treat than non-biofilm producers (3, 4). Biofilm production in CoNS is aided by a molecule called polysaccharide intercellular adhesin (PIA), encoded on *ica* gene operon, that

helps in intercellular adhesion (5). In addition to biofilm production, another important characteristic of the CoNS is the staphylococcal cassette chromosome *mec* (SCC*mec*), also present in *S. aureus*, the coagulase-positive staphylococci (6). Among other important side elements, SCC*mec* has the following two important components: the *mec* gene complex and the *ccr* gene complex. Till date, although SCC*mec* types I to XI have been described, only types I to VIII have been established; all these eleven types refer to *S. aureus* as the control strains (7). With respect to CoNS, types I to VIII were successfully detected by using the control types as references (8). The identification of several new types demonstrated the great genetic diversity of SCC*mec* and the need for developing classification schemes for SCC*mec* in CoNS (9). This review article covers the following topics:

- The epidemiology and clinical significance of CoNS
- The origin and elements of SCC*mec* types
- SCC*mec* types among CoNS species and their clinical significance
- The epidemiological data of SCC*mec* in CoNS
- Recent findings on new SCC*mec* types and possible future research

Epidemiology and Clinical Significance of Coagulase-Negative Staphylococci

More than 40 recognised CoNS species are part of the normal flora of the skin and mucous membranes (10). Species commonly isolated from human infections include *S. epidermidis*, *S. haemolyticus,* and *S. saprophyticus* in addition to other species that are occasionally isolated clinically, such as *Staphylococcus hominis*, *Staphylococcus warneri*, *Staphylococcus capitis*, *Staphylococcus simulans*, *Staphylococcus cohnii*, *Staphylococcus xylosus, Staphylococcus saccharolyticus,* and *S. lugdunensis* (11, 12). CoNS infections are usually associated with indwelling medical devices, especially in very young, old, and immuno-compromised patients since these infectious species are present abundantly on the skin and because of the high frequency of implantation of foreign devices in patients during hospitalisation (13, 14). They are recognised as the most frequent cause of prosthetic valve endocarditis, neurosurgical shunt infection, and infection of prosthetic orthopaedic devices because they are able to form biofilms enabling them to adhere to the inert surface of the devices, indirectly promoting increased resistance to antimicrobial agents (15). Moreover, urinary tract infections in young women are also caused by a particular CoNS species, *S. saprophyticus* (14). However, it was believed that CoNS are contaminants of blood rather than of true CoNS bacteraemia because their natural habitat is the skin. True CoNS bacteraemia and contaminant rates have been reported in bacteraemic patients worldwide. Mert et al. (16) had suggested laboratory criteria for true CoNS bacteraemia that included the assessment of multiple blood cultures positive for the same organisms and growth within 5 days where they found that the true CoNS bacteraemia rate in 249 episodes was 18.1%, consistent with the 6%–30% range as reported in these literatures; Souvenir et al. (17) reported that the prevalence of true CoNS bacteraemia was 24.7% in a total of 3276 blood cultures from 1433 patients; Finkelstein et al. (18) reported a prevalence of 30% in 137 episodes in 122 patients; Beekmann et al. (19) screened 960 consecutive patients with positive blood cultures and reported 22% significant bacteraemia rate. Al-Mazroea (20) concluded that although CoNS are true pathogens, they may act as contaminants in some cases. Therefore, patients with CoNS isolates in the blood cultures should be carefully evaluated before initiating any therapy to prevent the unnecessary use or overuse of antibiotics, especially vancomycin, to prevent the consequent increase in antibiotic resistance in hospitals.

Staphylococcal Cassette Chromosome *mec* Types

SCC*mec* is a mobile genetic element that carries *mecA* (methicillin-resistant gene) and other functional genes. Zong et al. (9) stated that SCC*mec* contains the following two essential components: the *mec* gene complex and the *ccr* gene complex. The *mec* gene complex consists of *mecA*, the regulatory genes, and the associated insertion sequences and has been classified into six different classes (A, B, C1, C2, D, and E) together with cassette chromosome recombinase (*ccr*) genes (*ccrC* or the pair of *ccrA* and *ccrB*) encoding recombinases that mediate the integration and excision of SCC*mec* into and from the chromosome. In addition, SCC*mec* also contains few other genes

such as insertion sequences, transposons, and plasmids (9). Turlej et al. (21) stated that the first SCC*mec* element was identified in 1999 followed by two additional SCC*mec* elements (22, 23). Resistance of staphylococci to methicillin and all *β*-lactam antibiotics is associated with the presence of the *mecA* gene that codes for the low affinity of a penicillin-binding protein, PBP2a, which is absent in susceptible staphylococci (24). In other words, the *mecA* gene is responsible for making staphylococci resistant to penicillin-like antibiotics. Hanssen and Sollid (25) stated in 2006 that till date, the only carrier described for *mecA* (encoding methicillin-resistance) in staphylococci was SCC*mec*. According to the International Working Group on the Staphylococcal Cassette Chromosome elements (7), SCC*mec* types are designated using Roman numerals followed by the *ccr* and *mec* gene complex; type I (1B) indicates a SCC*mec* harbouring a type 1 *ccr* and a class B *mec* gene complex. The other established designated SCC*mec* types are type II (2A), type

III (3A), type IV (2B), type V (5C2), type VI (4B), type VII (5C1), and type VIII (4A), as shown in Figure 1. Till date, eleven SCC*mec* types (I–XI) and subtypes have been described worldwide in staphylococci, and SCC elements that do not carry *mecA* (SCC non-*mec* types) but contain other characteristic genes such as capsule gene cluster, fusidic acid resistance, or the mercury-resistance operon have also been identified in the organisms (7, 26). Deurenberg et al. (27) performed molecular identifications of SCC*mec* type I to VI. Their study results show that types I (34.3 kb), IV (20.9 to 24.3 kb), V (28 kb), and VI (20.9 Kb) encode for resistance to *β*-lactam antibiotics only. In contrast, SCC*mec* types II (53.0 kb) and III (66.9 kb) possess multi-resistance properties because these elements contain additional drug resistance genes carried on integrated plasmids such as pUB110, pI258, and pT181, as well as a transposon (Tn554); plasmid pUB110 codes for kanamycin, tobramycin, and bleomycin resistance; pI258 codes for penicillin and heavy metals resistance;
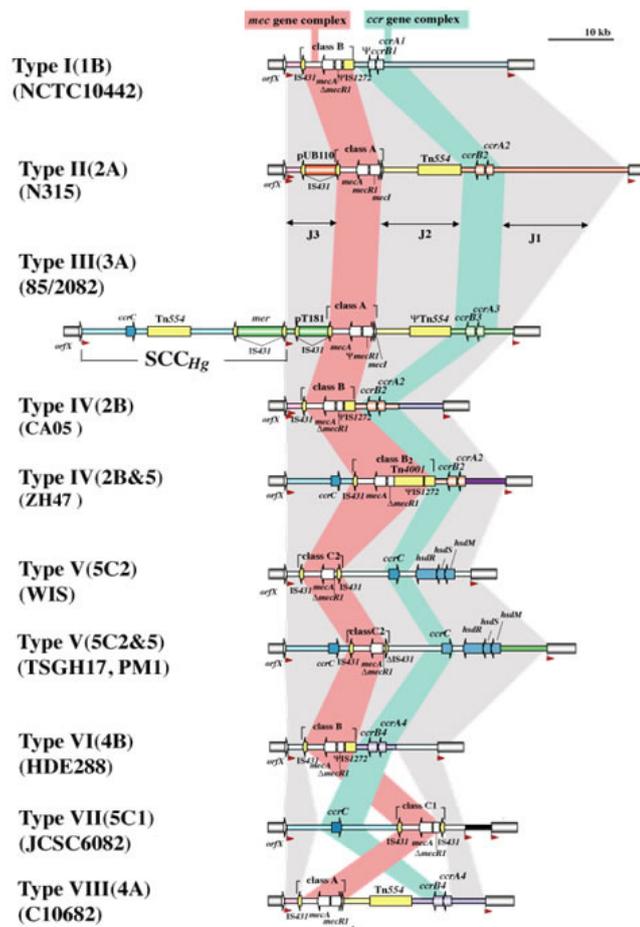

Figure 1. *mecA* and *ccr* locations of established SCC*mec* type I – VIII sequences

Source: Classification of staphylococcal cassette chromosome *mec* (SCC*mec*): Guidelines for reporting novel SCC*mec* elements. *Antimicrobial Agents and Chemotherapy*. 2009;**53(12)**:4961–4967.

pT181 codes for tetracycline resistance; and transposon Tn554 (carrying *ermA* gene) is responsible for inducible macrolide, lincosamide, and streptogramin (MLS) resistance.

Staphylococcal Cassette Chromosome mec Origin

Tulinski et al. (28) has stated that the origin of *SCCmec* is still unknown; however, it is believed that the *mecA* gene itself originated with one common precursor. Homologues of the *mecA* gene were discovered in *Staphylococcus sciuri* (29) and *Staphylococcus vitulinus* (30); however, these homologues are not located in a *mecA* complex as with SCCmec. Tsubakishita et al. (31) reported that 99%-100% of *mecA* gene sequence homology was found between *Staphylococcus fleurettii* and methicillin-resistant *S. aureus* (MRSA) strain N315 in addition to the presence of an almost identical structure of the *mecA* complex that resulted from additional sequence analysis. This shows that a direct precursor of the gene for MRSA is present in *S. fleurettii*, which is categorised under *S. sciuri* within the staphylococci. The possibility that *mecA* may originate from *S. fleurettii* strengthens the hypothesis that CoNS is the potential reservoir of the SCC*mec* from which MRSA acquired the elements (25). This is further supported by the fact that methicillin resistance among human clinical isolates is more prevalent in CoNS than in *S. aureus* (32, 33). In addition, the observation of an *in vivo* transfer of SCC*mec* from *S. epidermidis* to *S. aureus* indicates that CoNS could act as a source for SCC*mec* acquisition by *S. aureus* (34). Further, SCC*mec* types in CoNS are more heterogeneous than those in MRSA, as reported by Hanssen and Sollid (25) and Zhang et al. (35). These findings suggest the possibility of gene transfer in organisms other than staphylococci; therefore, the genes need to be studied in detail to achieve an accurate and adequate understanding of their properties and potential effects.

Staphylococcal Cassette Chromosome mec Types and their Clinical Significance among Coagulase-Negative Staphylococci Species

CoNS had been recognised as reservoirs of SCC*mec* based on several evidences of horizontal gene transfers of the SCC*mec* elements from CoNS to *S. aureus* as well as the diversity of the elements in the CoNS species (36–39). Various types of SCC*mec* from among ten selected CoNS species isolated from human and animal sources were observed and have been summarised in Table 1. Subtypes under SCC*mec* types I, II, III, and IV were distributed among *S. epidermidis*, *S. haemolyticus, S. capitis*, *S. sciuri,* and *S. warneri*. The three species *S. epidermidis*, *S. haemolyticus* and *S. capitis* had the widest SCC*mec* distribution with *S. epidermidis* possessing the most types. This is probably because *S. epidermidis* is globally the most commonly found species in hospital and community settings as well as in animal and livestock samples. Some studies could only detect one SCC*mec* type in one species. This may be because that particular species may have possessed only that particular SCC*mec* type during the research period. In addition, the SCC*mec* type distribution may also have been influenced by the type of samples and research locations. From this table, it can be seen that SCC*mec* types III, IV, and V were the most commonly distributed types among the ten selected CoNS species.

Associated with the potential genetic transfer of resistance elements, CoNS have been commonly identified in hospital-acquired infections whereby some of their SCC*mec* types have been clinically important, considering their association with antimicrobial resistance and infection risk for patients with indwelling devices, implants, prosthesis, and those subjected to invasive medical procedures (55). As stated by Marchant et al. (56), biofilm formation influences antibiotic resistance and infection persistence in association with central venous catheter (CVC) or other indwelling medical devices despite suitable antibiotic therapy. Zong et al. (9) had found that SCC*mec* types III, IV, and V isolated from clinical isolates were resistant to methicillin in addition to other antibiotics. By contrast, in a study done by Singh et al. (57), CoNS isolates with SCC*mec* types I showed high rates of multidrug resistance. On the other hand, a strong association was observed between SCC*mec* type I and III and non-*β*-lactam antibiotics resistance where the overall resistance was found to be more common in type I isolates, probably due to the higher proportion of those particular isolates than isolates with type III (58). These findings can help in observing the antibiotic resistance

Table 1. SCC*mec* types distribution among ten selected CoNS species

CoNS species	Source (s)	SCC*mec* type	Reference
S. epidermidis	Humans, cats, dogs, horses, pigs, poultry	I, IIa, IIb, III, III (variant), IV, IVa, IVb, IVc, IVd, IVe, IVg, V, VI, NT	Zhang et al. (35) Hanssen et al. (40) Malik et al. (41) Machado et al. (42) Jamaluddin et al. (43) Ruppé et al. (44) Ibrahem et al. (45) Garza-González et al. (46) Vanderhaeghen et al. (47) Kern & Perreten (48) Al-Bakri et al. (49)
S. haemolyticus	Humans, cats, horses, pigs	I, II, II.1, III, III (variant), IV, V, NT	Hanssen et al. (40) Machado et al. (42) Ruppé et al. (44) Ibrahem et al. (45) Garza-González et al. (46) Vanderhaeghen et al. (47) Kern & Perreten (48) Al-Bakri et al. (49) Pi et al. (50) Hammad et al. (51)
S. saprophyticus	Humans	III, NT	Higashide et al. (52) Söderquist & Berglund (53)
S. chromogenes	Humans	IV	Al-Bakri et al. (49)
S. hominis	Humans, dogs, pigs	I, III, IV, NT	Malik et al. (41) Machado et al. (42) Ibrahem et al. (45) Garza-González et al. (46) Vanderhaeghen et al. (47) Kern & Perreten (48) Al-Bakri et al. (49)
S. capitis	Humans, dogs	I, IA, II, III, IV, IVa, V, NT	Machado et al. (42) Ibrahem et al. (45) Kern & Perreten (48) Al-Bakri et al. (49)
S. lentus	Cattle, goats, sheep	III	Zhang et al. (35)
S. sciuri	Humans, cattle, goats, pigs, sheep	I, III, IIIA, V, VII, NT	Zhang et al. (35) Machado et al. (42) Vanderhaeghen et al. (47) Harrison et al. (54)
S. warneri	Humans, dogs, pigs, fish food	IV, IV.1, IVb, IVE, NT	Hanssen et al. (40) Malik et al. (41) Vanderhaeghen et al. (47) Kern & Perreten (48) Hammad et al. (51)
S. cohnii	Humans, dogs	NT	Kern & Perreten (48) Al-Bakri et al. (49)

NT: Non-typeable

patterns in CoNS although they may vary between different hospitals. Further molecular approaches are needed to generate more useful data on the molecular epidemiology of nosocomial CoNS isolates (55).

Epidemiological Data of Staphylococcal Cassette Chromosome *mec* in Coagulase-Negative Staphylococci

As known, SCC*mec* elements represent methicillin resistance. Till date, researchers have identified several structural differences in SCC*mec* elements via SCC*mec* typing in both, humans and animals. Table 2 summarises the distribution of SCC*mec* types in CoNS in several representative countries in the western and eastern parts of the world, including Malaysia. In humans, CoNS were isolated from samples such as urine, blood, nasal, and wound. These were also isolated from animals such as dogs, cats, chickens, and cattle.

Almost all SCC*mec* types have been detected in several western countries with type I being detected most commonly in the following four different countries: Brazil, Finland, Nigeria, and the United States of America (USA), while type VIII was detected most infrequently among the representative western countries. Subtypes of IVb and IVd were also found in Nigeria in addition to the new variants found in Finland and Portugal. A similar pattern was observed in eastern countries where type I was the most commonly distributed, while type VIII was most uncommon. New types such as IIa, IIb, Iva, and IVc were found in Japan; type VII was detected in Iran; and new variants were detected in Malaysia. When we compare the findings in Malaysia to those in the other eastern countries, it was observed that all globally established types (I to VIII) were detected in Malaysia in 2014. Regardless of the SCC*mec* types in both, the western and eastern regions, human samples were used more than animal samples because CoNS infection is a greater cause of concern in humans. Table 2 thus shows that till date, SCC*mec* typing data on animal and livestock samples are limited compared to that on human samples; consequently, typing on animal samples warrants further research in the future. Generally, human-associated CoNS include species such as *S. epidermidis*, *S. haemolyticus*, *S. hominis,* and *S. capitis* with *S. epidermidis* being the most commonly found and studied species, while animal-associated CoNS species include *Staphylococcus lentus*, *Staphylococcus caprae*, and *Staphylococcus carnosus* (2).

Horizontal transfer involving the *mecA* gene from CoNS to *S. aureus* had been observed. In addition, CoNS are known to be the reservoir of the resistance genes; therefore, the transfer might disseminate pathogenic staphylococci infections such as MRSA throughout the world (16, 34). It has been reported that animals infected with CoNS could be reservoirs for human infections through food or direct contact (63), and the horizontal transfer of SCC*mec* genes among CoNS could also occur between animals (35). However, to the best of our knowledge, gene transfers from animals to humans or vice versa have not yet been well researched and are still under investigation. Further studies on the possible transmission of SCC*mec* between CoNS from both, animal and human sources are warranted to gain a deeper understanding regarding these transfer mechanisms. Moreover, these findings together with microbial resistance programmes may assist hospitals and perhaps the respective regions to reduce the outbreaks or spread of the pathogenic clonal lineages of the CoNS species (64). In sum, it can be inferred that the variation in the SCC*mec* types may be influenced by geography, particular situational settings, and sources, and the differences in the data regarding the distribution types across countries are possibly due to the fact that these research studies were unable to detect certain types or intentionally detected only the types of interest.

Table 2. Distribution of SCC*mec* types among CoNS isolated from human and animal sources in several countries

Region/Country	Source	SCC*mec* type	Reference
West			
USA	Animal	I, III, IV, V	Zhang et al. (35)
Nigeria	Human	I, IVb, IVd, NT	Vitali et al. (38)
Finland	Human	I, II, IV, V, New	Ibrahem et al. (45)
Sweden	Human	III, NT	Söderquist and Berglund (53)
Brazil	Human	I, II, III, IV, (I and III)	Machado et al. (59)
Portugal	Human	VI, VIII, NT, New	Bouchami et al. (60)
Poland	Human	V, NT	Szczuka et al. (61)
East			
Malaysia	Human	I, II, III, IV, V, VI, VIII, NT, New	Sani et al. (8)
China	Human	II, III, V	Zong et al. (9)
Australia	Animal	I, III, IV, V	Malik et al. (41)
Japan	Human	I, IIa, IIb, III, IVa, IVb, IVc, IVd, V, NT	Jamaluddin et al. (43)
India	Human	I, II, III, IV, NT	Ghosh et al. (55)
Iran	Human	I, II, III, IV, V, VII, NT	Najar et al. (62)

NT: Non-typable

Recent Finding on New Staphylococcal Cassette Chromosome *mec* Type

In September 2015, Wu et al. (65), reported a novel *ccr* gene, *ccrC2*, in the SCC*mec* of *S. aureus* isolate BA01611, which showed 62.6%–69.4% sequence identity to all published *ccrC1* sequences. The *ccrC2* gene was found to be mainly located among CoNS and could be found in staphylococcal isolates from the USA, France, Germany, and China. Wu et al. (65) categorised the *ccr* gene complex under type 9, while the SCC*mec* of BA01611 was indicated as a novel type designated as type XII (9C2). This novel SCC*mec* element in BA01611 was covered by a pseudo SCC element 22 (ΨSCCBA01611) that carries a truncated *ccrA1*. Excision of the SCC elements and a composite SCC from the chromosome was done based on the 24 extra-chromosomal circular intermediates detection. These researchers recommended including the *ccrC2* gene and typing 9 *ccr* gene complexes during the SCC*mec* typing method revision.

Possible Future Research

Research on SCC*mec* in *S. aureus* may be in its advanced stage; however, the understanding of *SCCmec* in CoNS is still poor. Data regarding hospital and community-acquired infections were insufficient, especially in Malaysia. This needs to be highlighted since the prevalence and severity of CoNS infections is on the rise. Due to the complex nature and increasing diversity of SCC, more studies need to be conducted, particularly for CoNS, to further investigate the association between the SCC*mec* types and risk factors, to observe and compare the predominant SCC*mec* types in samples other than blood, and to identify novel *mec* genes and allelic variants as well as SCC-encoded virulence-associated genes. These could provide a better understanding of the behavioural aspects of CoNS.

Conclusion

This paper gives a review of the distribution of SCC*mec* types among several CoNS species isolated in some countries. CoNS are now as concerning as *S. aureus* in terms of causing serious infections in hospital and community settings; in addition, CoNS are evidenced as the reservoir of SCC*mec* elements; therefore, their advanced phenotypic and genotypic studies (particularly on SCC*mec* properties) are crucial for their further characterisation and better understanding. The findings of these can be implemented in the enhancement of infection control, prevention, or the development of new, potential antimicrobial agents, enhancing the

knowledge, scope, and skills in the fields of science, technology, and medicine.

Authors' Contributions

Conception and design: HS, RI, ASJ, TZMTJ
Analysis and interpretation of the data: HS
Drafting of the article: HS, RI, ASJ
Critical revision of the article for important intellectual content: HSABS, RI, ASJ, TZMTJ
Final approval of the article: HS
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Obtaining funding: RI
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