A Review of Staphylococcal Cassette Chromosome \textit{mec} (SCC\textit{mec}) Types in Coagulase-Negative Staphylococci (CoNS) Species

Huda SABER, Azmiza Syawani JASNI, Tengku Zetty Maztura TENGKU JAMALUDDIN, Rosni IBRAHIM

Department of Medical Microbiology and Parasitology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor Darul Ehsan, Malaysia

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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 \textit{mec} (SCC\textit{mec}), plays an important role in staphylococci pathogenesis. Among CoNS, SCC\textit{mec} has been studied less frequently than \textit{Staphylococcus aureus} (coagulase-positive staphylococci). A recent study (8) conducted in Malaysia successfully detected SCC\textit{mec} type I to VIII as well as several new combination patterns in CoNS species, particularly \textit{Staphylococcus epidermidis}. However, data are still limited, and further research is warranted. This paper provides a review on SCC\textit{mec} types among CoNS species.

Keywords: CoNS, epidemiology, SCC\textit{mec} types, \textit{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 \textit{Micrococcaceae} family, CoNS were believed to be less virulent than \textit{Staphylococcus aureus} (1). However, CoNS have been recently established as one of the major nosocomial pathogens, with \textit{Staphylococcus epidermidis} and \textit{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; \textit{Staphylococcus saprophyticus} is responsible for up to 10% of uncomplicated urinary tract infections in young women; \textit{Staphylococcus schleiferi}, \textit{Staphylococcus lugdunensis}, and \textit{S. haemolyticus} are involved in native valve endocarditis. Newly discovered species such as \textit{Staphylococcus pettenkoferi} and \textit{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 \textit{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 (SCCmec), also present in S. aureus, the coagulase-positive staphylococci (6). Among other important side elements, SCCmec has the following two important components: the mec gene complex and the ccr gene complex. Till date, although SCCmec 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 SCCmec and the need for developing classification schemes for SCCmec in CoNS (9).

This review article covers the following topics:

- The epidemiology and clinical significance of CoNS
- The origin and elements of SCCmec types
- SCCmec types among CoNS species and their clinical significance
- The epidemiological data of SCCmec in CoNS
- Recent findings on new SCCmec 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

SCCmec is a mobile genetic element that carries mecA (methicillin-resistant gene) and other functional genes. Zong et al. (9) stated that SCCmec 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 SCCmec into and from the chromosome. In addition, SCCmec also contains few other genes.
such as insertion sequences, transposons, and plasmids (9). Turlej et al. (21) stated that the first SCCmec element was identified in 1999 followed by two additional SCCmec 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 SCCmec. According to the International Working Group on the Staphylococcal Cassette Chromosome elements (7), SCCmec types are designated using Roman numerals followed by the ccr and mec gene complex; type I (1B) indicates a SCCmec harbouring a type 1 ccr and a class B mec gene complex. The other established designated SCCmec 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 SCCmec 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 SCCmec 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, SCCmec 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, pl258, and pT181, as well as a transposon (Tn554); plasmid pUB110 codes for kanamycin, tobramycin, and bleomycin resistance; pl258 codes for penicillin and heavy metals resistance;

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

Source: Classification of staphylococcal cassette chromosome mec (SCCmec): Guidelines for reporting novel SCCmec 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 SCCmec 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 SCCmec from *S. epidermidis* to *S. aureus* indicates that CoNS could act as a source for SCCmec acquisition by *S. aureus* (34). Further, SCCmec 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 SCCmec based on several evidences of horizontal gene transfers of the SCCmec elements from CoNS to *S. aureus* as well as the diversity of the elements in the CoNS species (36–39). Various types of SCCmec from among ten selected CoNS species isolated from human and animal sources were observed and have been summarised in Table 1. Subtypes under SCCmec 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 SCCmec 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 SCCmec type in one species. This may be because that particular species may have possessed only that particular SCCmec type during the research period. In addition, the SCCmec type distribution may also have been influenced by the type of samples and research locations. From this table, it can be seen that SCCmec 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 SCCmec 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 SCCmec 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 SCCmec types I showed high rates of multidrug resistance. On the other hand, a strong association was observed between SCCmec 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. SCCmec types distribution among ten selected CoNS species

| CoNS species          | Source(s)                                | SCCmec type        | Reference                                                                 |
|-----------------------|------------------------------------------|--------------------|---------------------------------------------------------------------------|
| *S. epidermidis*      | Humans, cats, dogs, horses, pigs, poultry| I, II, 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, SCCmec elements represent methicillin resistance. Till date, researchers have identified several structural differences in SCCmec elements via SCCmec typing in both, humans and animals. Table 2 summarises the distribution of SCCmec 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 SCCmec 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 SCCmec 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, SCCmec 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 SCCmec 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 SCCmec 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 SCCmec 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 SCCmec types among CoNS isolated from human and animal sources in several countries

| Region/Country | Source | SCCmec type | Reference |
|----------------|--------|-------------|-----------|
| West USA       | Animal | I, III, IV, V | Zhang et al. (35) |
|                | Human  | I, IVb, IVd, NT | Vitali et al. (38) |
| Nigeria        | Human  | I, II, IV, V, New | Ibrahim et al. (45) |
| Finland        | Human  | III, NT | Söderquist and Berglund (53) |
| Sweden         | Human  | I, II, III, IV, (I and III) | Machado et al. (59) |
| Brazil         | Human  | VI, VIII, NT, New | Bouchami et al. (60) |
| Portugal       | Human  | V, NT | Scezuka et al. (61) |
| Poland         | Human  | I, II, III, IV, V, VI, VIII, NT, New | Sani et al. (8) |
| East Malaysia  | Human  | I, II, III, IV, V, VI, VIII, NT, New | Zong et al. (9) |
| China          | Human  | I, III, IV, V | Malik et al. (41) |
| Australia      | Animal | I, IIa, IIb, III, IVa, IVb, IVc, IVd, V, NT | Jamaluddin et al. (43) |
| Japan          | Human  | I, II, III, IV, NT | Ghosh et al. (55) |
| India          | 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 SCCmec 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 SCCmec of BA01611 was indicated as a novel type designated as type XII (9C2). This novel SCCmec 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 SCCmec typing method revision.

Possible Future Research

Research on SCCmec 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 SCCmec types and risk factors, to observe and compare the predominant SCCmec 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 SCCmec 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 SCCmec elements; therefore, their advanced phenotypic and genotypic studies (particularly on SCCmec 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.

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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
Provision of study materials or patients: RI, ASJ, TZMTJ
Obtaining funding: RI
Collection and assembly of data: HS

Correspondence

Dr Rosni Ibrahim
Master of Pathology (MPath) (Universiti Kebangsaan Malaysia), Medical Doctor (MD) (University Sains Malaysia)
Department of Medical Microbiology and Parasitology, Faculty of Medicine & Health Sciences,
Universiti Putra Malaysia, 43400 UPM Serdang, Selangor Darul Ehsan, Malaysia.
Tel: 03 89472363
Fax: 03 89413802
E-mail: rosni.ibrahim@upm.edu.my

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