UNIVERSITI PUTRA MALAYSIA

ANTIMICROBIAL SUSCEPTIBILITY PATTERN AND DISTRIBUTION OF STAPHYLOCOCCAL CASSETTE CHROMOSOME mec AMONG METHICILLIN-RESISTANT COAGULASE-NEGATIVE STAPHYLOCOCCI

HUDA BINTI SABER ABU BAKR SALEH

FPSK(M) 2018 30

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By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

April 2018

DEDICATION

I would like to specially dedicate this work to my beloved late father, my mother, husband and the other family members that have been motivating and supporting me from the beginning till the end of this project. I would not be this successful without their supportive souls.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the Degree of Master of Science

ANTIMICROBIAL SUSCEPTIBILITY PATTERN AND DISTRIBUTION OF STAPHYLOCOCCAL CASSETTE CHROMOSOME *mec* AMONG METHICILLIN-RESISTANT COAGULASE-NEGATIVE STAPHYLOCOCCI

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April 2018

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Coagulase-negative staphylococci (CoNS) are notorious in causing nosocomial infections. *Staphylococcus epidermidis* is deemed the most significant species infecting human, apart from *Staphylococcus haemolyticus* and *Staphylococcus chromogenes*. In Malaysia, there is an increasing trend of antimicrobial resistance among CoNS whereby more than 50% has been reported as methicillin-resistant coagulase-negative staphylococci (MR-CoNS) which these organisms harbour *mecA* gene which is acquired by a mobile genetic element in staphylococci called staphylococcal cassette chromosome *mec* (SCC*mec*). This study aims to investigate species distribution among 100 MR-CoNS, to determine antimicrobial susceptibility pattern among the species and to detect their SCC*mec* types.

Coagulase-negative staphylococci (CoNS) isolated from blood cultures were collected from Microbiology laboratory, Hospital Serdang in year 2016 and proceeded to phenotypic identification by gram-staining, catalase and coagulase test. Species identification was done by using API® Staph kit. Antimicrobial susceptibility testing (AST) was performed by using Kirby-Bauer method with nine antibiotic discs and was interpreted following Clinical and Laboratory Standards Institute (CLSI) 2016. Detection of SCC*mec* was performed by using multiplex polymerase chain reaction (PCR). *Staphylococcus epidermidis* (n=56, 56%) was the most common species isolated in this recent study, followed by *S. haemolyticus* (n=19, 19%), *S. chromogenes* (n=12, 12%), *Staphylococcus xylosus* (n=6, 6%), *Staphylococcus hominis* (n=5, 5%), *Staphylococcus capitis* (n=1, 1%) and *Staphylococcus cohnii* (n=1, 1%). All isolates were resistant to cefoxitin (n=100, 100%) and penicillin (n=100, 100%). More than 80% of the isolates were resistant to erythromycin and 70% were resistant to fucidic acid. All isolates were sensitive to vancomycin. A total of 54 (54%) isolates harboured SCC*mec* type IVa (n=32, 32%) in which was widely distributed in *S. epidermidis* (n=27, 48.2%). Fifteen (15%) isolates showed combination types which the most

common was type I & IVa (n=9, 9%) and another 31 strains (31%) were non-typeable. Type IVa was observed to have multiple antibiotic resistance with high rates of resistance towards erythromycin (n=32, 100%) followed by fucidic acid (n=25, 78.1%) and clindamycin (n=24, 75%).

In conclusion, *S. epidermidis* was the most common isolated species. Apart from penicillin, high percentages of resistance towards erythromycin and fucidic acid were observed in this recent study. This is probably due to the high usage of these antibiotics in outpatient clinical setting. Type IVa was the most detected SCC*mec* with multiple antibiotic resistance harbouring.

Keywords: Antimicrobial susceptibility pattern, *mecA*, MR-CoNS, SCC*mec*

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Master Sains

CORAK KERINTANGAN ANTIMIKROB DAN TABURAN KASET KROMOSOM STAFILOKOKUS *mec* DI KALANGAN STAFILOKOKUS KOAGULASE-NEGATIF BERINTANGAN TERHADAP METISILIN

Oleh

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Stafilokokus koagulase-negatif (CoNS) terkenal dalam menyebabkan jangkitan nosokomial. Di samping *Staphylococcus haemolyticus* dan *Staphylococcus chromogenes*, *Staphylococcus epidermidis* dikatakan sebagai spesies paling signifikan yang menjangkiti manusia, Di Malaysia, terdapat peningkatan kecenderungan kerintangan antimikrob dalam kalangan CoNS dimana lebih daripada 50% telah dilaporkan sebagai CoNS yang mempunyai kerintangan terhadap metisilin (MR-CoNS) yang mengandungi gen *mecA* yang mengekod 'penicillin-binding protein 2a' (PBP2a) yang mempunyai pengikatan pertalian yang rendah kepada semua antibiotik β-lactam. Gen tersebut diperolehi oleh elemen genetik bergerak dalam stafilokokus yang dipanggil kaset kromosom stafilokokus (SCC*mec*). Tujuan kajian ini adalah untuk menyiasat taburan spesis dikalangan 100 MR-CoNS, menentukan corak kerintangan antimikrob spesies dan jenis-jenis SCC*mec*.

Stafilokokus koagulase-negatif (CoNS) yang telah diisolasi daripada kultur-kultur darah dikumpulkan dari makmal Mikrobiologi, Hospital Serdang dalam tahun 2016 dan diteruskan kepada pengenalpastian fenotipik menggunakan pewarnaan 'gram', ujian katalase dan koagulase. Pengenalpastian spesies dilakukan dengan menggunakan kit API® Staph. Ujian kerintangan antimikrob (AST) telah dijalankan menggunakan kaedah 'Kirby-Bauer' berserta sembilan disk antibiotik dan ditafsirkan mengikut 'Clinical and Laboratory Standards Institute' (CLSI) 2016. Pengesanan SCC*mec* dijalankan dengan menggunakan 'multiplex polymerase chain reaction (PCR)'. *Staphylococcus epidermidis* (n=56, 56%) merupakan spesies yang paling banyak diisolasi dalam kajian baru-baru ini, diikuti oleh *S. haemolyticus* (n=19, 19%), *S. chromogenes* (n=12, 12%), *Staphylococcus xylosus* (n=6, 6%), *Staphylococcus hominis* (n=5, 5%), *Staphylococcus capitis* (n=1, 1%) dan *Staphylococcus cohnii* (n=1, 1%). Semua isolat rintang kepada sefoksitin (n=100, 100%) dan penisilin (n=100, 100%). Lebih daripada 80% isolat rintang kepada eritromisin (n=87, 87%) dan 70% rintang

kepada asid fusidik. Semua isolat sensitif kepada vankomisin. Sebanyak 54 (54%) isolat mengandungi SCC*mec* jenis IVa (n=32, 32%) dimana ianya merupakan jenis yang paling banyak ditaburkan dalam *S. epidermidis* (n=27, 48.2%). Lima belas (15%) isolat menunjukkan jenis kombinasi dimana jenis yang mendominasi adalah jenis I & IVa (n=9, 9%) dan 31 (31%) 'strain' yang lain tidak dapat dijeniskan. Jenis IVa diperhatikan mempunyai kerintangan terhadap pelbagai antibiotik dengan kadar peratusan kerintangan yang tinggi terhadap eritromisin (n=32, 100%), diikuti oleh asid fusidik (n=25, 78.1%) dan klindamisin (n=24, 75%).

Secara keseluruhannya, *S. epidermidis* merupakan spesies yang paling banyak diisolasi. Selain daripada penisilin, peratusan kerintangan yang tinggi terhadap eritromisin dan asid fusidik diperhatikan dalm kajian baru-baru ini. Hal ini adalah berkemungkinan kerana penggunaan antibiotik ini secara kerap dalam tetapan klinikal pesakit luar. Jenis IVa merupakan jenis SCC*mec* yang paling banyak dikesan dengan kandungan kerintangan terhadap pelbagai antibiotik.

Kata kunci: Corak kerintangan antibiotik, *mecA*, MR-CoNS, SCC*mec*

ACKNOWLEDGEMENTS

First and foremost, all praises to **ALLAH S.W.T**, my one and only Creator for leading me to this challenging yet fantastic journey of research. Without His guidance, I would not be able to finish this race.

I humbly wish to express my special gratitude and endless appreciation to my supportive supervisor, **DR. ROSNI IBRAHIM** for piquing my interest in working with clinical isolates, and for helping me in the beginning stages of this project until its completion. Regardless her busyness, she still managed to guide me patiently and being so understanding on my hard times and problems. Not to forget my co-supervisors, **DR. AZMIZA SYAWANI JASNI** and **DR. TENGKU ZETTY MAZTURA TENGKU JAMALUDDIN** for their priceless guidance, critics, comments and motivation throughout the course of this thesis. I would also like to thank other lecturers for their encouragement, advices, and supports along the process.

I would also like to wholeheartedly acknowledge Professor Dr. Keiichi Hiramatsu and Associate Professor Dr. Yuki Uehara from Juntendo University (Tokyo), Professor Dr. Robert Daum from University of Chicago (Illinois), Professor Dr. Anders Rhod Larsen from Statens Serum Institut (Copenhagen), Professor Dr. Herminia de Lencastre from The Rockefeller Univeristy (New York) and Associate Professor Dr. Neoh Hui Min from UKM Medical Molecular Biology Institute (Kuala Lumpur) for giving permission and assistance in providing SCC*mec* types controls. Special thanks to Dr. Tengku Zetty Maztura Tengku Jamaluddin for helping me to obtain the controls. I would never finish my research without their assistance.

Nevertheless, huge thanks to the head of Microbiology Unit, Pathology Department of Hospital Serdang, Dr. Lailatul Akmar Mat Nor as well as other staff for their cooperation and guidance throughout a year of sample collection. I would really like to appreciate National Institutes of Health (NIH) and Medical Research and Ethics Committee (MREC) UPM for providing ethical approvals to conduct my research as well as IPS Grant numbered 9507200 for funding this project.

A bunch of thanks to my JMPP mates who have helped me a lot in understanding my project, showing me how to handle equipment in the laboratory, and willing to teach me correct methods while doing the experiments. Not forgetting, my beloved husband, fabulous mother and families for supporting and helping me in widen my knowledge on science. Last but not least, I would like to thank those from other faculties for their advices, supports, guidance and knowledge-sharing as well as who have been involved in this project directly or indirectly.

I certify that a Thesis Examination Committee has met on 17 April 2018 to conduct the final examination of Huda binti Saber Abu Bakr Saleh on her thesis entitled "Antimicrobial Susceptibility Pattern and Distribution of Staphylococcal Cassette Chromosome *mec* among Methicillin-Resistant Coagulase-Negative Staphylococci" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

ADH	Arginine DiHydrolase
AST	Antimicrobial Susceptibility Testing
ATCC	American Type Culture Collection
BA	Blood agar
bp	Basepair
Buffer BV	DNA Binding Buffer
Buffer DV	Phase-partition Buffer
Buffer G-A	Lysis Buffer
Buffer G-B	Protein-removal Buffer
Buffer W1	Wash Buffer
Buffer W2	Desalting Buffer
CAUTIs	Catheter Associated Urinary Tract Infections
ccr	Cassette Chromosome Recombinase
CDC	Centre for Disease Control and Prevention
CLI	Clindamycin
CLSI	Clinical Laboratory Standards Institute
CoNS	Coagulase-negative staphylococci
CRBSIs	Catheter-related Bloodstream Infections
CSF	Cerebrospinal Fluid
CVC	Central Nervous Catheter
dH_2O	Distilled water
DNA	Deoxyribonucleic acid
dNTP	Deoxyribonucleotide triphosphate
EDTA	Ethylenediaminetetraacetic acid

ERM	Erythromycin
FA	Fucidic acid
O_2	Free Oxygen
FBRIs	Foreign Body-related Infections
FOX	Cefoxitin
g	Gram
GM	Gentamicin
h	Hour
HCW	Health Care Workers
H_2O	Water
H_2O_2	Hydrogen peroxide
HVS	High Vaginal Swab
Ica	Intercellular Adhesion
ICUs	Intensive Care Units
IWG-SCC	International Working Group on the Classification of Staphylococcal Cassette Chromosome Elements
kb	Kilobase
kDa	Kilodalton
L	Litre
M	Molar
MDR	Multidrug resistance
mecA	Methicillin resistance
mg	Miligram
mg/ml	Milligram per mililitre
MIC	Minimum Inhibitory Concentration
min	Minute

mL	Mililitre
MLST	Multi Locus Sequence Typing
mM	Milimolar
MR-CoNS	Methicillin-resistant coagulase-negative staphylococci
MREC	Medical Research and Ethics Committee
MRSA	Methicillin-resistant *Staphylococcus aureus*
MRSE	Methicillin-resistant *Staphylococcus epidermidis*
MRSH	Methicillin-resistant *Staphylococcus haemolyticus*
msrA	Methionine Sulfoxide Reductase A
NaCL	Sodium chloride
NC	Negative control
NCBI	National Center of Biotechnology Information
ng	Nanogram
NHSN	National Healthcare Safety Network
NICUs	Neonatal Intensive Care Units
NIH	National Institutes of Health
NIT	Nitrate
ORFs	Open reading frames
PAL	Alkaline Phosphatase
PBP	Penicillin binding Protein
PBP2a	Penicillin-binding Protein 2a
PC	Positive control
PCN	Penicillin
PCR	Polymerase chain reaction
PFGE	Pulse Field Gel Electrophoresis

pH	Potential of hydrogen
PIA	Polysaccharide Intercellular Adhesion
PJIs	Prosthetic Joint-associated Infections
PYR	Pyrrolidonyl Arylamidase
RA	Rifampin
rcf	Relative centrifugal force
rpm	Revolutions per minute
rRNA	Ribosomal ribonucleic acid
SCC*mec*	Staphylococcal cassette chromosome *mec*
SPSS	Statistical Package for the Social Sciences
SXT	Trimethoprim/sulfamethoxazole
TBE	Tris-Borate-EDTA
TSB	Trypticase soy broth
URE	Urease
UTIs	Urinary Tract Infections
UV	Ultraviolet
V	Volts
VAN	Vancomycin
VP	Voges Proskauer
µg	Microgram
µg/mL	Microgram per mililitre
µL	Microlitre
µm	Micrometer
%	Percent
^{o}C	Degree Celcius

CHAPTER 1

INTRODUCTION

1.1 Study Background

Staphylococci which are members of Micrococcaceae family, are gram-positive bacteria with single or grape-like cluster arrangements, possessing catalase-positive characteristics. Besides being normally isolated from mucous membranes and skin of humans and animals, staphylococci can also be found in environment, water and food (Widerström, 2010). Categorized into coagulase-positive staphylococci (CoPS) and coagulase-negative staphylococci (CoNS) groups, *Staphylococcus aureus* is the significant CoPS species while *Staphylococcus epidermidis* is the most significant CoNS (Kloos & Bannerman, 1994; Widerström, 2010). Since CoNS are major in colonizing skin and mucous membranes of mammals, they frequently contaminate blood cultures and cause uncertainty in determining their significance (Al-Mazroea, 2009; Elzi *et al*., 2012).

Presently, CoNS has been existing as one of the major nosocomial pathogens (Becker *et al*., 2014). They have the capability to cause infections include foreign body-related infections (FBRIs), preterm newborns infections and endocarditis (Becker *et al*., 2014). This is because CoNS posssess a virulence factor called biofilm that assist them to adhere to medical devices in hospitals (Fredheim *et al*., 2009). Accumulation of biofilm is caused by *ica* genes which involve in the biosynthesis of polysaccharide intercellular adhesion (PIA) molecules (Namvar *et. al.,* 2013). Biofilm-producing CoNS have been observed to become resistant to multiple antibiotics classes such as lincosamides and macrolides (Otto, 2008; Fredheim *et al*., 2009). Serious nosocomial infections can occur if the hospital environment is colonized by multidrug-resistance biofilm-forming CoNS (Wojtyczka *et al*., 2014). Major concern among clinicians is towards the increasing numbers of methicillin and multidrug-resistant strains (Becker *et al*., 2014). Widely spread in hospitals, most commonly isolated methicillin-resistant coagulase-negative staphylococci (MR-CoNS) species include *S. epidermidis*, *Staphylococcus haemolyticus, Staphylococcus saprophyticus* and several more (Mehdinejad *et al*., 2008). These organisms harbour *mecA* gene that encodes penicillin-binding protein 2a (PBP2a) which contributes to low binding to all β-lactam antibiotics (Hartman & Tomasz, 1984; Becker *et al*., 2014). The gene is acquired by staphylococcal casette chromosome *mec* (SCC*mec*) (Wielders *et al.,* 2002). This mobile genetic element possesses two important components which are *mec* gene and cassette chromosome recombinase (*ccr)* gene complexes; *mec* gene complex consisting of *mecA* with classes of A, B, C1, C2, D and E, the regulatory genes and associated insertion sequences express methicillin resistance function whereas *ccr* and a few surrounding genes assist SCC*mec* integrate into and out from the chromosome (IWG-SCC, 2009; Zong *et al.*, 2011). In addition, there are also J regions (for SCC*mec* subtypes determination) and several non-essential components which may carry additional antimicrobial resistance determinants (IWG-SCC, 2009). Specific combinations of *mec* gene and *ccr* gene complexes produce different types of SCC*mec* which include types I-XI (Zong *et al.*,

2011). Type III, IV and V were prevalently found in MR-CoNS and an isolate may possess more than one type (Zong *et al.*, 2011). According to Barbier *et al*. (2010), SCC*mec* displays more polymorphous structure in MR-CoNS in terms of *ccr-mec* combinations compared to methicillin-resistant *Staphylococcus aureus* (MRSA).

In Malaysia, data related to these organisms is limited. Thus, this study aims to determine the distribution of MR-CoNS species isolated from clinical blood cultures and their SCC*mec* types as well as to observe the antimicrobial susceptibility pattern and its relatedness with the identified SCC*mec* types. The outcomes from this research particularly the SCC*mec* genes findings, can be a set of preliminary data that can be used for further research.

1.2 Problem Statement

In Malaysia, there is an increasing trend of antimicrobial resistance among CoNS whereby 50% have been reported as MR-CoNS (Sani *et al*., 2011). Causing more severe infections until today besides being resistant to various antibiotics, it is understood that CoNS and especially MR-CoNS have appeared to be important nosocomial pathogens. Considering that the data related to these organisms are limited in Malaysia, particulary on SCC*mec* among MR-CoNS in hospitals, more studies should be conducted as the findings could contribute in providing local data as well as assisting clinicians in managing MR-CoNS infections.

1.3 Objectives

1.3.1 General Objective

This study attempted to determine antimicrobial susceptibility pattern and SCC*mec* type distribution among MR-CoNS species isolated from blood cultures in Hospital Serdang.

1.3.2 Specific Objectives

1. To determine the distribution of MR-CoNS species from blood culture isolates
2. To determine the antimicrobial susceptibility pattern among the isolated MR-CoNS species
3. To detect the SCC*mec* types among the isolated MR-CoNS species
4. To study the antimicrobial susceptibility pattern among the SCC*mec* types

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