UNIVERSITI PUTRA MALAYSIA

MOLECULAR HETEROGENEITY OF METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS ISOLATED FROM HUMANS, ANIMALS AND ENVIRONMENTAL SURFACES

ERKIHUN AKLILU WOLDEGIORGIS

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By

ERKIHUN AKLILU WOLDEGIORGIS

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

March 2010

DEDICATION

I would like to dedicate this thesis to my late father Aklilu Woldegiorgis Tekleab, 'the Moses' whose inspirations drove me all the way.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Master of Science

MOLECULAR HETEROGENEITY OF METHICILLIN-RESISTANT *STAPHYLOCOCOCCUS AUREUS* ISOLATED FROM HUMANS, ANIMALS AND ENVIRONMENTAL SURFACES

By

ERKIHUN AKLILU WOLDEGIORGIS

MARCH 2010

Chairperson : Assoc. Prof. Dr. Zunita Zakaria, PhD

Faculty : Veterinary Medicine

Methicillin-resistant *Staphylococcus aureus* (MRSA) has long been known to cause nosocomial infections worldwide since its emergence in the early 1960s. Nowadays, this organism is found to prevail in the wider community and is becoming an emerging problem in veterinary medicine. This study aimed to determine the molecular heterogeneity of the MRSA isolates obtained from human, pets (cats and dogs), and the environment. Swab samples were collected from 103 veterinary medicine students, 28 University Veterinary Hospital (UVH) staff, 100 pets (50 cats and 50 dogs), and 200 environmental surfaces. Conventional biochemical tests, Staphytect Plus® identification kit, growth on selective media, antibiotic sensitivity test (AST), and minimum inhibitory concentration (MIC) determination were used for phenotypic identification while *mec*A gene detection was used for genotypic detection of MRSA. A total of 43 MRSA were successfully isolated from the different sources. Prevalence rates were 23.3% (24/103), 7.14 (2/28), 8.0% [(8/100), 6.0% (5/50) cats and 10.0% (5/50) dogs], 4.5% (9/200) in

students, UVH staff, pets and environment respectively. All MRSA isolates were found to be resistant to three or more antimicrobial agents. The oxacillin MICs ranged from 1.5 µg/mL to ≥256 µg/mL with the majority (86.0%), having MICs of ≥ 4 µg/mL. The *mec*A gene was found to be present in 83.7% (36/43) of the isolates. Although *mec*A gene amplification has been accepted as the gold standard for MRSA detection, several other factors are known to confer *S. aureus* resistance against methicillin. Molecular fingerprinting by pulsed-field gel electrophoresis (PFGE) classified the isolates into three clusters with 26 pulsotypes and three subtypes. Few isolates from the same source category shared similar or close relationship with each other. However, the finger print patterns for the isolates among the different source categories appeared to be too heterogeneous and sporadic. The multi locus sequencing typing (MLST) analyses grouped the selected 10 isolates (5 from human, 3 from pets, and 2 from environmental) into 5 clonal complexes (CCs) and two singletons comprising nine sequence types (STs). Two STs, ST59 and ST5 were previously reported from neighboring countries such as Singapore and Thailand indicating a regional spread of the clones with the potential contribution of human movement. Staphylococcal protein A gene (*spa*) sequence typing revealed nine distinct *spa* types including one new *spa* type (t5697). Combinations of MLST and *spa* typing methods have revealed the molecular heterogeneity within and in between most of the tested MRSA isolates. The molecular fingerprints of the isolates revealed similarities between human and pets and human and the environment and these are suggestive of the inter-transmission and spread of the MRSA clones from one of the sources to the other. Since there is no database on the molecular fingerprints of MRSA isolates in the country, the findings from this study serve as a baseline data for future studies and to design comprehensive and contextual control strategies to contain further spread of MRSA.

Abstrak tesis yang dikemukakan kepada Senat Univeristi Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

KEPELBAGAIAN MOLEKULAR *STAPHYLOCOCOCCUS AUREUS* RINTANG METISILIN YANG DIPENCILKAN DARIPADA MANUSIA, HAIWAN DAN PERMUKAAN PERSEKITARAN

Oleh

ERKIHUN AKLILU WOLDEGIORGIS

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Staphylococcus aureus rintang terhadap metisilin (MRSA) telah lama diketahui sebagai penyebab jangkitan nosokomial di seluruh dunia semenjak kemunculannya pada awal 1960an. Pada masa kini, organisma ini didapati menular dalam komuniti dan menyebabkan jangkitan antara komuniti. Kajian ini menumpu kepada penelitian terhadap kepelbagaian molekular yang wujud di antara MRSA yang dipencilkan daripada manusia, haiwan kesayangan (kucing dan anjing) dan persekitaran. Persampelan yang telah dijalankan ke atas 103 pelajar kedoktoran veterinar, 28 pegawai Hospital Veterinar Universiti (UVH), 100 haiwan kesayangan (50 ekor kucing and 50 ekor anjing), dan 200 permukaan persekitaran. Ujian biokimia konvensional, kit pengenalpastian Staphytect Plus®, pertumbuhan di atas media selektif, ujian kepekaan antibiotik (AST), dan ujian inhibisi minima antibiotik (MIC) telah digunakan untuk pengenalpastian MRSA secara fenotipik sementara penentuan kehadiran gen *mec*A itu

digunakan sebagai pengenalpastian genotipik. Sejumlah 43 MRSA berjaya dipencilkan daripada punca yang berbeza. Kadar prevalen adalah 23.3% (24/103), 7.14 (2/28), 8% [(8/100), 6% (5/50) anjing dan 10% (5/50) kucing], 4.5% (9/200) untuk pelajar, pegawai UVH, haiwan kesayangan dan persekitaran. Kesemua pencilan MRSA adalah rintang terhadap tiga atau lebih agen antimikrobial. Bacaan MIC bagi oksasilin adalah dari 1.5 µg/mL ke ≥256 µg/mL dengan majoriti pencilan (86%), memberikan bacaan MIC ≥ 4 µg/mL. Gen *mec*A dikesan pada 83.72% (36/43) pencilan MRSA. Walaupun kehadiran *mec*A merupakan "gold standard" bagi pengenalpastian MRSA, beberapa faktor lain juga memainkan peranan dalam kadar kerintangan *S. aureus* terhadap metisilin. Pencirian molekular menggunakan "pulsed-field gel electrophoresis" (PFGE) mengklasifikasikan pencilan kepada 3 kluster dengan 26 pulsotip and 3 subtip. Beberapa pencilan dari punca yang sama didapati mempunyai hubungan yang rapat antara satu sama lain. Walaubagaimanapun, pentipan molekular bagi pencilan daripada punca berbeza didapati terlalu heterogenus dan sporadik. Analisis 'multi locus sequencing typing' (MLST) membahagikan 10 pencilan terpilih (5 dari manusia, 3 dari haiwan kesayangan, dan dua daripada persekitaran) kepada 5 kompleks klonal (CCs) and dua "singletons" merangkumi 9 tip jujukan (STs). Dua STs, ST59 and ST5 telah pun dilaporkan dari negara jiran seperti Singapura dan Thailand menunjukkan bahawa penyebaran klon mungkin berpunca daripada aktiviti pergerakan manusia. Pentitipan jujukan gen Staphylococcal protein A (*spa*) mendedahkan 9 tip *spa* termasuk satu tip *spa* novel (t5697). Kombinasi kaedah MLST dan pentitipan *spa* typing telah dapat menunjukkan heterogenisiti di antara pencilan MRSA. Pentipan molekular pencilan menunjukkan persamaan di antara pencilan manusia dan haiwan kesayangan dan juga di antara manusia dan persekitaran mencadangkan transmisi dan sebaran klon MRSA dari

satu punca kepada yang lain. Oleh kerana tiada pengkalan data yang wujud untuk pentipan molekular MRSA di negara ini, maka data hasil daripada kajian ini dapat dijadikan sebagai garis dasar untuk kajian lanjut dan juga dalam merumus strategi dalam membendung penularan MRSA.

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I certify that a Thesis Examination Committee has met on 4 March 2010 to conduct the final examination of Erkihun Aklilu Woldegiorgis on his thesis entitled "Molecular Heterogeneity of Methicillin-Resistant *Staphylococcus aureus* isolated from humans, animals and environmental surfaces" 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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DECLARATION

I hereby declare that the thesis is based on my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously, or concurrently, submitted for any other degrees at Universiti Putra Malaysia or at any other institution.

ERKIHUN AKLILU WOLDEGIORGIS

Date: 8 March 2010

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LIST OF ABBREVIATIONS

agr	Accessory gene regulator
yqiL	Acetyl coenzyme A acetyltransferase
AIDS	Acquired Immunodeficiency Syndrome
AL	Alkaline Lysis
α	Alpha
ATCC	American Type Culture Collection
APHIS	Animal and Plant Health Inspection Service
AST	Antibiotic Sensitivity Test
bps	Base pairs
BURST	Based Upon Related Sequence Typing
β	Beta
blaR1	Beta lactamase regulatory protein R1
blaR2	Beta lactamase regulatory protein R2
blaI	Beta lactamase repressor protein
blaZ	Beta lactamase Z
BMC	Bio-Med Central
BORSA	Borderline oxacillin-resistant *Staphylococcus aureus*
BSA	Bovine serum albumin
BHIA	Brain-Heart Infusion Agar
BHIB	Brain-Heart Infusion Broth
BSAC	British Society for Antimicrobial Chemotherapy
arcC	Carbamate kinase
CDC	Centers for Disease Control and Prevention
CHIP	Chemotaxis inhibitory proteins
CLSI	Clinical and Laboratory Standards Institute
CC	Clonal complex
CoNS	Coagulase-negative *Staphylococcus*
CFU	Colony forming units
CA-MRSA	Community-acquired methicillin-resistant *Staphylococcus aureus*

CHEF	Contour-clamped homogeneous electric field
^{o}C	Degree Celcius
dATP	Deoxyadenosine triphosphate
dCTP	Deoxycytidine triphosphate
dGTP	Deoxyguanosine triphosphate
DNA	Deoxyribonucleic acid
dNTP	Deoxyribonucleotide triphosphate
dTTP	Deoxythymidine triphosphate
DLV	Double locus variant
ESP	EDTA-sarcosine-proteinase buffer
eBURST	Electronic Based Upon Related Sequence Types
SEA-SEQ	Enterotoxins serotypes A through Q
EMRSA	Epidemic Methicillin-resistant *Staphylococcus aureus*
EDTA	Ethylenediaminetetraacetic acid
EARSS	European Antimicrobial Resistance Surveillance System
EFSA	European Food Safety Authority
EJCAP	European Journal of Companion Animal Practice
fem	Factors essential for methicillin resistance
FIGE	Field-inversion gel electrophoresis
Fab	Fragment antigen-binding
FEMS	Federation of European Microbiological Society
Fc	Fragment crystallizable region
*mec*A	Gene coding for penicillin-binding protein 2a
GI	Genomic islands
glpF	Glycerol kinase
gmk	Guanylate kinase
HA-MRSA	Hospital- acquired methicillin-resistant *Staphylococcus aureus*
h	Hour(s)
HCl	Hydrochloric acid
IgG	Immunoglobulin G
IU	international unit

JPEG	Joint Photographic Experts Group
kDa	Kilodalton
L	Litre
EC	Lysis buffer
MSA	Mannitol salt agar
Mbp	Mega base pair(s)
MRS	Methicillin-resistant staphylococci
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
µg	Micro gram
µL	Micro Liter
µM	Micro molar
MSCRAMMS	Microbial surface components recognizing adhesive matrix molecules
mA	Milli ampere
mg	Milli gram
mL	Milli litre
mM	Milli molar
MIC	Minimum inhibitory concentration
min	Minute(s)
M	Molar
MHA	Muller-Hinton agar
MDR	Multi-drug-resistant
MLEE	Multilocus enzyme electrophoresis
MLST	Multilocus sequence typing
MLVA	Multilocus variable number of tandem repeats analysis
GlcNAc	N-acetylglucosamine
MurNAc	N-acetylmuramic acid
NCCLS	National Committee for Clinical Laboratory Standards
NNIS	National Nosocomial Infection Surveillance System (USA)
NSAR	National Surveillance on Antimicrobial Resistance (Malaysia)

ND	Not determined
ORSAB	Oxacillin Resistance Screening Agar Base
PVL	Panton-Valentine Leukocidin
PBP	Penicillin-binding protein
%	Percentage(s)
PMSF	Phenyl methyl sulfonyl fluoride
pta	Phosphate acetyltransferase
PBS	Phosphate buffered saline
PNAS	Proceeding of the National Academy of Society (USA)
PCR	Polymerase chain reaction
PFG	Pulsed-field gel
PFGE	Pulsed-field gel electrophoresis
Rep-PCR	Repeat sequence primed polymerase chain reaction
RE	Restriction endonuclease
RFLP	Restriction fragment length polymorphism
rpm	Revolution per minutes
s	Second(s)
ST	Sequence type
*Sma*I	*Serratia marcescens*I
aroE	Shikimate dehydrogenase
SLV	Single locus variant
SPCA	Society for the Prevention of Cruelty to Animals
NaCl	Sodium chloride
SDS	Sodium dodecyl Sulfate
spp	Species
SCC*mec*	Staphylococcal cassette chromosome *mec*
SPA	Staphylococcal Protein A
spa	*S. aureus* protein A encoding gene
Taq	*Thermus aquaticus*
Tiff	Tagged Image File Format
TSS	Toxic shock syndrome

TSST-1	Toxic shock syndrome toxin-1
Tn	Transposon
tpi	Triosephosphateisomerase
TBE	Tris-borate-EDTA buffer
TE	Tris-EDTA buffer
TEN	Tris-EDTA-NaCl
UV	Ultraviolet
UPM	Universiti Putra Malaysia
USM	Universiti Sains Malaysia
UVH	University Veterinary Hospital
UPGMA	Unweighted pair group method using the arithmetic averages
VISA	Vancomycin Intermediate *Staphylococcus aureus*
VRSA	Vancomycin-Resistant *Staphylococcus aureus*
VNTR	variable number of tandem DNA repeat.
V	Volt
WMJ	Wincosin Medical Journal
WTA	Wall teichoic acid
w/v	Weight per volume

Abbreviations for Antibiotics

AK	Amikacin
AMC	Amoxycillin-Clauvulanic acid
AML	Amoxicillin
FOX	Cefoxitin
DO	Doxycycline Hydrochloride
E	Erythromycin
CN	Gentamicin
IPM	Impenem
MET	Methicillin
MH	Minocycline
OX	Oxacillin
RD	Rifampicin
S	Streptomycin
TE	Tetracycline
VA	Vancomycin

CHAPTER ONE

INTRODUCTION

Staphylococcus aureus is a frequent cause of human infections and is one of the most important nosocomial pathogens (Fenner *et al*., 2008). While a variety of staphylococcal species are present on or in clinically normal individuals, staphylococci are also opportunistic pathogens causing community-associated diseases in humans and animals worldwide (O'Mahony *et al*., 2005; Kloos, 1980). Diseases caused by staphylococci in animal species include suppurative diseases, mastitis, arthritis, and urinary tract infections among others (Waldvogel, 1990). In humans, a wide array of clinical syndromes ranging from minor skin lesions such as boils and carbuncles, to potentially fatal conditions such as endocarditis and toxic shock syndrome are caused by staphylococcus species (Murray, 2005; Todd, 2005). *Staphylococcus aureus* is the pathogen of great concern because of its intrinsic virulence, its ability to cause a diverse array of life threatening infections, and its capacity to adapt to different environmental conditions (Waldvogel, 2000; Lowy, 1998). *Staphylococcus aureus* strains are also frequently resistant to most of the commonly used antimicrobial agents, including the aminoglycosides, macrolids, chloramphenicols, tetracyclines and fluoroquinolones (Lee, 2003). According to Clinical Laboratory Standards Institution (CLSI), formerly known as National Committee for Clinical Laboratory Standards (NCCLS), methicillin-resistant staphylococci should be considered resistant to all cephalosporines, cephems, and other β-lactams, such as ampicillin-sulbactam, amoxacillin-clavulanic acid, piperacillin-

tazobactam, and the carbapenams regardless of the *in vitro* test obtained with those agents (CLSI/NCCLS, 1997).

Methicillin-resistant *S. aureus* was first reported in 1961 and has since become an important cause of nosocomial and, increasingly, community-acquired infections worldwide (Brown *et al*., 2005; Chambers, 2001). In many industrialized nations and parts of the Far East, 40-60% of all hospital isolates of *S. aureus* are now resistant to penicillin or are MRSA (Fluit *et al*., 2001) and there is a fear and clear sign that MRSA continues to increase in prevalence in both the community and hospitals (Hawkey, 2008). In Malaysia, the prevalence of MRSA increased from the range of 10-25% in 1985-1986 to more than 40% in 1996 according to surveys conducted in several hospitals (Rohani *et al,* 2000; Lim, 1988). Moreover, a recent study has reported 43.7% of community-associated MRSA (CA-MRSA) from infectious samples isolated within 48 hours of hospital admission (Neela *et al*., 2008a). As MRSA isolates are often resistant to numerous commonly used antimicrobial agents, they can represent a major problem in the hospital environment, causing a variety of serious nosocomial infections which are extremely difficult to treat (Strommenger *et al*., 2006a). Vancomycin has been the antibiotic of choice to treat MRSA infections, and the emergence of vancomycin-nonsusceptible *S. aureus* in recent years is a great public health concern and has made therapy of MRSA infections even more challenging (Palavecino, 2007).

In recent years MRSA infections have been reported among horses, pigs, cattle, sheep, cats, dogs, and rabbits (Walther *et al*., 2008), and has been considered as an emerging

problem in small animal and equine practices (Leonard and Markey, 2008). Companion animals such as dogs, cats, and horses have been implicated more frequently as potential reservoirs of MRSA (Loeffler *et al*., 2005). Jacklyn (2006) indicated the presence of the bacteria at 1.9% prevalence rate in cats and dogs in Malaysia. Two studies conducted by Cafi *et al*. (1994) and Scott *et al*. (1988) suggested that animals may serve as a reservoir for infection of humans. On the other hand, a recent comprehensive review regarding MRSA in dogs and cats concluded that the risk to human health appears to be small but that a survey of MRSA in animals was required (Duqquet and Nuttal, 2004). Moreover, MRSA strains have been found to survive for long periods on many different surfaces in the hospital environment and in private homes (Neely and Maley, 2000; de Boer *et al*., 2006). Wagenvoort *et al*. (2000) showed that outbreak strains survived for a longer period in the surroundings than sporadic MRSA strains. Bartels *et al*. (2008) found that MRSA strains of different *spa* types were able to survive on hospital furniture and fabrics for at least one week and also found that MRSA could survive for at least one month on upholstered chairs.

Clinical isolates of MRSA carry a complex, yet poorly understood resistance mechanism (de Lencastre *et al*., 1991). Methicillin resistance in *S. aureus* is mainly attributed to the presence of *mec*A gene which encodes the production of an additional protein-binding protein (PBP) named PBP2'/PBP2a. According to Cefai *et al*. (1994), the PBP2a is present in more than 90% of MRSA isolates. Accordingly, detection of *mec*A, the gene encoding the production of PBP2'/PBP2a, is considered to be the most reliable method for identifying methicillin-resistant staphylococci (Bekkaoui *et al*., 1999; Cloney *et al*.,

1999; Chambers, 1997). However, despite the ubiquitous presence of *mec*A gene, MRSA isolates has been shown to have tremendous variation in MICs for the majority of cells (Chambers, 1997; Tomasz *et al*., 1991). Cultures of MRSA can be heterogeneous; they can contain a variety of subpopulations for which the MICs can range from very low to very high. It was shown that these complex modes of phenotypic expression are strain specific and appeared to be under genetic control (Tomasz *et al*., 1991). Hence, the resistance characteristics of MRSA is not totally attributed to *mec*A gene, since other chromosomal genes that are physically distinct from *mec*A are necessary for full expression of resistance (Chambers, 1997; Berger-Bachi *et al*., 1992).

With the discovery of vancomycin-resistant *S. aureus* (VRSA) or vancomycin-intermediate *S. aureus* (VISA) isolates and the ability of MRSA isolates to be resistant to almost all available antibiotics used, prompt and accurate identification and epidemiological typing of the MRSA isolates are crucial (Stranden *et al*., 2003). To this effect, a large number of molecular methods have been developed for typing MRSA strains (Stranden *et al*., 2003). Molecular typing of MRSA is performed to identify clones with known epidemiology and pathogenic characteristics, or to define the source and scope of an outbreak so as to prevent further spread and infection. Although there are many different genotyping methods currently in use, the most popular is PFGE following *Sma*I digestion of genomic DNA (Maslow *et al*., 1993). But this method is technically demanding, time-consuming, and expensive (Stranden *et al*., 2003). It is not suitable for longer-term, national or global epidemiological studies, and it lacks inter-laboratory reproducibility (Robinson and Enright, 2004). Among the various DNA

sequence-based methods that have been developed to overcome these limitations, MLST (Robinson and Enright, 2004) and *spa* typing have been shown to be effective and rapid methods for typing MRSA (Moodely *et al*., 2006).

In Malaysia, limited studies have been carried out on MRSA in the veterinary settings. No data exists on the occurrence of MRSA in veterinary professionals and students, and veterinary hospital environments. Knowledge on the molecular heterogeneity of isolates from human, pets and the environment is also lacking. It is hypothesized that MRSA isolated from staff of University Veterinary Hospital (UVH), veterinary medicine students, pets (cats and dogs), and environmental premises of the small animal clinic at UPM are molecularly homogenous.

The present study aimed to:

1. determine the occurrence of MRSA in veterinary medicine students, veterinary personnel, pets and their related environments.
2. determine the antimicrobial resistance patterns and MICs of the isolated MRSA.
3. characterize the MRSA isolates and determine their molecular heterogeneity.

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