UNIVERSITI PUTRA MALAYSIA

DETECTION OF BETA-LACTAMASE GENES AND ANTIBIOTIC SUSCEPTIBILITY PROFILES OF Staphylococcus aureus ISOLATES IN A HOSPITAL IN MALAYSIA

BAKHTIYAR MAHMOOD HAMASALIH

FPSK(M) 2017 48

DETECTION OF BETA-LACTAMASE GENES AND ANTIBIOTIC SUSCEPTIBILITY PROFILES OF *Staphylococcus aureus* ISOLATES IN A HOSPITAL IN MALAYSIA

By

BAKHTIYAR MAHMOOD HAMASALIH

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

June 2017

COPYRIGHT

DEDICATION

I would like to dedicate this work to my beloved parents, family members and those who taught, motivated and helped me throughout my study. Without my parents support I could not accomplished this work.

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

DETECTION OF BETA-LACTAMASE GENES AND ANTIBIOTIC SUSCEPTIBILITY PROFILES OF *Staphylococcus aureus* ISOLATES IN A HOSPITAL IN MALAYSIA

By

BAKHTIYAR MAHMOOD HAMASALIH

June 2017

Chairman : Tengku Zetty Maztura binti Tengku Jamaluddin, MBChB, PhD
Faculty : Medicine and Health Sciences

Staphylococcus aureus is a versatile pathogen causing a variety of infections. Resistance to β-lactam antibiotics among *S. aureus* isolates has been attributed to the bla system detection. The bla system consists of three main components which are *blaR1*, a sensor signal transducer gene, *blaZ*, structural gene encoding β-Lactamase enzyme, and *blaI*, a repressor gene. The aim of this study is to detect the presence of *blaR1* gene and to determine its relationship with phenotypic resistance of *S. aureus*. Identification of 128 isolates of *S. aureus* was carried out based on colony morphology, Gram stain, catalase and coagulase tests. All isolates were subjected to susceptibility test of commonly used antibiotics by disc diffusion method. Resistant strains toward cefoxitin were considered as phenotypic methicillin resistant *S. aureus* (MRSA) and were subjected to further determination of vancomycin Minimum Inhibitory Concentration (MIC) by E-test. *BlaR1* gene detection among all isolates was done by polymerase chain reaction (PCR). For phenotypic MRSA strains, resistance towards methicillin was further confirmed by *mec*A gene detection.

All non urine isolates were sensitive to vancomycin and rifampin via disc diffusion method. Followed by trimethoprim/sulfamethoxazole (n=122, 98.4%). Whereas, all urine isolates were sensitive to vancomycin, trimethoprim/sulfamethoxazole, gentamicin and nitrofurantoin. Widespread of resistance against penicillin group (n=107, 83.6%) was detected, followed by cefoxitin (n=32, 25%) reported as phenotypic MRSA. PCR revealed all (n=107, 83.6%) penicillin group resistant isolates harboured *blaR1* gene. Whereas, all (n=32, 100%) phenotypic MRSA strains harboured *mec*A gene. Five penicillin susceptible strains were positive for *blaR1* gene, four had slightly larger amplicon size compared to *blaR1* gene and one had similar amplicon size with the *blaR1* gene. Penicillin and oxacillin E-test, nitrocefin disc test, bla system genes and *mec*A gene detection were conducted for these five strains. Sequencing analysis was performed for these five penicillin susceptible strains.

Vancomycin E-test revealed two (n=2, 6.25%) MRSA strains were intermediate to vancomycin and one strain with reduced susceptibility (MIC 3 μg/mL). All five penicillin susceptible *blaR1* positive strains were susceptible to penicillin and oxacillin by E-test and negative for nitrocefin test. Only one strain (A56) was positive for *blaZ* and *mec*A gene. Sequencing and homology analysis of all five penicillin susceptible *blaR1* positive strains did not have any similarity with any *blaR1* gene sequence in NCBI website. However, four strains had 100% correspondence with *S. aureus* strain AUS0325 genome assembly. Conversely, sequencing result for *blaZ* gene of strain A56 and *blaR1* gene of representative penicillin resistant strains had 100% and 99% similarity with *S. aureus* strain N315 *blaZ* and *blaR1* genes respectively. Statistical analysis found significance association of *blaR1* gene with phenotypic resistant of *S. aureus* to beta lactam antibiotics. There was no significant association seen for other antibiotics. In conclusion, in this study *Staphylococcus aureus* strains were resistant to penicillin, followed by cefoxitin and erythromycin. All penicillin resistant strains harboured *blaR1* gene, and all cefoxitin resistant strains harboured *mec*A gene. There may be a role for *blaR1* gene detection among *S. aureus* to confirm beta lactam resistance, which would be useful to aid in managing infected patients efficiently.

Keywords: Antibiotic resistance, *blaR1*, *S. aureus*, MRSA

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

PENGESANAN GEN-GEN BETA-LACTAMASE DAN PROFIL KERINTANGAN BAKTERIA *Staphylococcus aureus* YANG DIASINGKAN DARI SEBUAH HOSPITAL DI MALAYSIA

Oleh

BAKHTIYAR MAHMOOD HAMASALIH

Jun 2017

Pengerusi : Tengku Zetty Maztura binti Tengku Jamaluddin, MBChB, PhD
Fakulti : Perubatan dan Sains Kesihatan

Staphylococcus aureus adalah patogen serba boleh yang menyebabkan pelbagai jenis jangkitan. Kerintangan terhadap antibiotik kumpulan beta-lactam (β-lactam) telah dikaitkan dengan pengesanan sistem bla, yang terdiri daripada tiga komponen utama iaitu gen *blaR1* sejenis transduser gen yang memberi isyarat untuk kerintangan, gen *blaZ* yang mengekod struktur enzim beta-lactamase (β-lactamase), dan gen *blaI* sebagai gen repressor. Tujuan kajian ini adalah untuk mengesan kehadiran gen *blaR1* dan untuk menentukan hubungannya dengan kerintangan antibiotik beta lactam oleh *S. aureus*. Sebanyak 128 *S. aureus* telah dikaji, dan ujian fenotipik dilakukan berdasarkan morfologi koloni, Gram stain, ujian enzim katalase dan enzim koagulase. Ujian kerintangan antibiotik yang biasa digunakan dalam suasana klinikal dengan kaedah cakera penyebaran turut dilakukan. Kerintangan terhadap sefoksitin dianggap sebagai kerintangan fenotipik terhadap metisilin, iaitu methicillin resistance *S. aureus* (MRSA). Selanjutnya bagi fenotipik MRSA, pengesahan kerintangan terhadap vankomisin dilakukan melalui E-test (CLSI, 2016). Tindak balas rantai polimerase (PCR) telah dilakukan untuk mengesan kehadiran gen *blaR1* bagi semua *S. aureus*. Bagi fenotipik MRSA pula, pengesanan gen *mec*A dilakukan. Penisilin dan oksasilin E-test, ujian cakera nitrocefin, pengesanan gen sistem bla dan pengesanan gen *mec*A telah dijalankan bagi lima *S. aureus* yang tiada kerintangan terhadap penisilin tetapi positif untuk gen *blaR1*. Analisa urutan genetik juga dilakukan untuk lima bakteria *S. aureus* tersebut.

Ujian kerintangan antibiotik melalui kaedah cakera penyebaran menunjukkan semua *S. aureus* daripada sampel selain air kencing adalah sensitif kepada vankomisin, rifampin (n =124, 100%), diikuti oleh trimethoprim/sulfamethoxazole (n =122, 98.4%). Kesemua *S. aureus* daripada sampel air kencing adalah sensitif terhadap vankomisin, trimethoprim/sulfamethoxazole, gentamisin dan nitrofurantoin (n =4, 100%). Peratusan kerintangan terhadap penisilin adalah agak tinggi (n =107, 83.6%),

dan diikuti oleh sefoksitin (n =32, 25%). Vankomisin E-test menunjukkan dua (n =2, 6.25%) strain MRSA mempunyai kerintangan intermediat untuk vankomisin dan satu strain mempunyai suseptibiliti berkurangan (MIC 3 μg/mL). Gen *blaR1* telah dikesan dalam 107 (83.6%) *S. aureus* yang mempunyai kerintangan terhadap penisilin termasuk dua strain yang diasingkan daripada air kencing. Semua (n =32, 100%) strain fenotipik MRSA mempunyai gen *mec*A. Kesemua lima strain *S. aureus* yang sensitif terhadap penisilin yang mempunyai gen *blaR1* masih sensitif terhadap penisilin dan oksasilin melalui E-test, dan negatif untuk ujian nitrocefin. Hanya satu strain (A56) yang positif untuk gen *blaZ* dan *mec*A. Analisis homologi urutan genetik lima strain *S. aureus* yang masih sensitif terhadap penisilin, tidak mempunyai persamaan dengan mana-mana urutan gen *blaR1* dalam laman web NCBI. Walaubagaimanapun, empat strain mempunyai 100% persamaan dengan genom *S. aureus* AUS0325. Sebaliknya, hasil penjujukan untuk gen *blaZ* bagi A56 dan gen *blaR1* bagi strain wakil mempunyai persamaan 100% dan 99% dengan gen *blaZ* dan gen *blaR1 S. aureus* N315 masing-masing. Analisis statistik mendapati kewujudan gen *blaR1* adalah berhubungkait dengan kerintangan fenotipik *S. aureus* terhadap antibiotik beta-lactam. Tidak ada hubungan yang signifikan dilihat untuk kumpulan antibiotik lain. Kesimpulannya, majoriti *Staphylococcus aureus* dalam kajian ini mempunyai kerintangan terhadap penisilin, diikuti oleh sefoksitin dan eritromisin. Semua strain yang mempunyai kerintangan terhadap penisilin mempunyai gen *blaR1*, dan semua strain yang mempunyai kerintangan terhadap sefoksitin mempunyai gen *mec*A. Peranan untuk mengesan gen *blaR1* bagi strain *S. aureus* untuk mengesahkan kerintangan beta-lactam secara PCR, adalah lebih cepat dan berpotensi untuk membantu doktor merawat jangkitan *S. aureus* dengan lebih efisyen.

Kata kunci: rintangan antibiotik, *blaR1*, *S. aureus*, MRSA

ACKNOWLEDGEMENTS

All praises are for Allah, the most gracious and most merciful who taught human with means of pen how to write and taught man which he knew not. I am greatly thankful to Almighty Allah who has enabled me to undertake this task and complete it successfully.

First and foremost, I would like to express my heartfelt appreciation and special gratitude to my supervisor **DR. TENGKU ZETTY MAZTURA BINTI TENGKU JAMALUDDIN** who offered tremendous support and took time out of her busy schedule to offer very useful advice on all aspects of this work from the study design to the laboratory work and final write up. I highly appreciate her encouragement and effort in proofreading my thesis.

I would also like to gratefully acknowledge the effort of **DR. ROSNI BINTI IBRAHIM**, a member of my supervisory committee for her valuable advices, guidance and scholarly criticism throughout my study time. I thank her for the role she played towards the successful completion of my research. I would like to extend my especial thanks to Associate Professor Dr. Malina Osman for her kindness and support during my data analysis. My thanks also extend to all the staffs in the Department of Medical Microbiology and Parasitology at UPM for their moral support by all means during my study.

I also would like to acknowledge Professor Dr. Keiichi Hiramatsu (Juntendo University, Tokyo) and Dr. Neoh Hui Min at (UKM Medical Molecular Biology Institute (UMBI)) for their permission and assistance in providing positive controls for *blaR1* gene. I appreciate Dr. Lailatul Akmar Mat Nor head of Pathology Department and all staff of Medical Microbiology laboratory of Hospital Serdang for their support and cooperation during sample collection.

I would like to extend my deepest gratitude and sincere to my beloved parents for their encouragement and prays throughout my life for my success, may Allah bless them forever. I have no words to express my feelings of gratitude to my family members for all of their support and help to undertake this work. Allah may continue to reward you abundantly. My appreciation is also extended to my colleagues in the Department of Medical Microbiology and Parasitology for their assistance.

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

Tengku Zetty Maztura binti Tengku Jamaluddin, MBChB, PhD
Medical Lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Rosni binti Ibrahim, MD, MPath (Microbiology)
Medical Lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

_____

ROBIAH BINTI YUNUS, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date:

Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

Signature: _____
Name of Chairman of Supervisory Committee: Dr. Tengku Zetty Maztura binti Tengku Jamaluddin

Signature: _____
Name of Member of Supervisory Committee: Dr. Rosni binti Ibrahim

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AMP	Ampicillin
AST	Antimicrobial Susceptibility Test
ATCC	American Type Culture Collection
bp	Base pair
ccr	Chromosomal cassette recombinant
CDC	Centre for Disease Control and Prevention
CLI	Clindamycin
CLSI	Clinical Laboratory Standards Institute
CONS	Coagulase negative staphylococcus
CRF	Coagulase reacting factor
DNA	Deoxyribonucleic acid
dsDNA	Double stranded DNA
EARSS	European Antimicrobial Surveillance System
EDTA	Ethylene Diamine Tetra acetic Acid
ERM	Erythromycin
E-test	Epsilometer test
FA	Fusidic acid
FOX	Cefoxitin
g	Gram
GM	Gentamycin
H_2O_2	Hydrogen peroxide
HA-MRSA	Hospital acquired MRSA
ICUs	Intensive Care Units
L	Litre
LZD	Linezolid
Mbp	Mega base pairs
MDR	Multidrug-Resistant

mg	Milligram
MGEs	Mobile genetic elements
MIC	Minimum Inhibitory Concentration
mL	Millilitre
MRSA	Methicillin Resistant *Staphylococcus aureus*
MSA	Mannitol salt agar
MSCRAMMs	Microbial surface components recognizing adhesive matrix molecules
MSSA	Methicillin Sensitive *Staphylococcus aureus*
NC	Negative control
NCBI	National Centre for Biotechnology Information
ng	Nanogram
NIT	Nitrofurantoin
NNIS	National Nosocomial Infection Surveillance
NSAR	National Surveillance of Antibiotic Resistance
ORFs	Open reading frames
PAP-AUC	Population analysis profile – area under curve
PBP	Penicillin binding protein
PBPa	Alternative penicillin binding protein
PC	Positive control
PCN	Penicillin
PCR	Polymerase Chain Reaction
PVL	Panton Valentine Leukocidine
RA	Rifampin
SCC*mec*	Staphylococcal Cassette Chromosome *mec* element
SPSS	Statistical Package for the Social Science
SSTI	Skin and Soft Tissue Infection
SXT	Trimethoprim / Sulfamethoxazole
TBE	Tris Borate-EDTA

TSB	Trypticase soy broth
TSST-1	Toxic shock syndrome toxin-1
UK	United Kingdom
UPM	Universiti Putra Malaysia
US	United State
UV	Ultra violet
VAN	Vancomycin
VISA	Vancomycin intermediate *Staphylococcus aureus*
VRSA	Vancomycin Resistant *Staphylococcus aureus*
µg	Micro gram
µL	Microlitre
µm	Micromoler

CHAPTER 1

INTRODUCTION

1.1 Background of the Study

Staphylococcus aureus as a major pathogen of humans is an issue of global healthcare concern. Although considered as an opportunistic pathogen, as it colonizes its host asymptomatically, it occasionally causes a range of infections from the relatively less severe minor skin and soft tissue infections (SSTI) to the life-threatening scalded skin syndrome, bacteraemia and pneumonia. Originally, to a variety of *S. aureus* infections, penicillin was the choice drug. However, the emergence of beta lactamase producing strains in 1942 made them penicillin-resistant. Nowadays, over 95% of *S. aureus* from humans are proved to be penicillin-resistant (Fuda *et al.*, 2005; Tang *et al*., 2014).

The *blaZ* is a gene that encodes for the *S. aureus* beta lactamase enzyme. The *blaZ* gene and its repressor *blaI* together with the *blaR1*, a signal transducer sensor protein, form an aggregate or cluster either within the bacterial chromosome or on a plasmid (Pence *et al*., 2015; Holden *et al.*, 2004). In a situation where the organism is not exposed to a beta lactam antibiotic the *blaZ* becomes repressed by the *blaI* which is a DNA repressor. This is brought about by binding to the DNA conserved motif TACA/TGTA, that is located in the *blaZ* promoter region (Llarrull *et al.*, 2010; Safo *et al.*, 2005).

The drugs of choice for the treatment of *S. aureus* infections were initially the beta lactam antibiotics, but a slightly different strain of this organism, the methicillin resistant *Staphylococcus aureus* (MRSA) emerged in 1961, and proved resistant to all the members of whole class of the β-lactam. For more than half a century, MRSA has been a clinical problem all over the world. The set of genes within the operons bla and *mec* are the molecular basis for the incidentally inducible wide resistance of the MRSA. The protein *blaR1* (or the cognate *mecR1*) is a transducer of β-lactam antibiotic signal/sensor. It sends the information on the antibiotic presence in the cytoplasmic surrounding, using a process not clearly defined or understood (Boudreau *et al.*, 2015).

The strains of MRSA are importantly studied pathogens especially in the hospitals (McClure *et al.*, 2006; Trindade *et al.*, 2005). These bacterial pathogens are presently isolated from both hospital patients and members of community (Kowalski *et al.*, 2005; Vourli *et al.*, 2007). Many clinical studies have shown that the strains of MRSA are more virulent than their susceptible counterparts, the methicillin susceptible *S. aureus* (MSSA), on the basis of mortality rates (Rozgonyi *et al.*, 2007). The number of dead patients due to MRSA infections is greatly higher than that due to MSSA (Melzer *et al.*, 2003). In MRSA, mediation of resistance to methicillin is brought about by the presence of beta lactam antibiotic low affinity 78-kDa penicillin binding protein

PBP2 (or PBP2a). The gene *mec*A encodes for PBP2a (Moreillon, 2008). The location for *mec*A gene is a mobile genetic element (from 21kb to 67kb) known as staphylococcal cassette chromosome *mec* elements (SCC*mec*) (Ammons *et al.*, 2010). Penicillin binding proteins, the PBPs, normally have strong affinity for the β-lactam ring. However, in the strains of MRSA another PBP, the PBP2a is generated by the presence of *mec*A gene. This PBP2a has a very low affinity for binding to the beta-lactam antibiotics. This consequently leads to some beta lactam antibiotics like methicillin losing their ability to destroy the bacterial cell wall (Malachowa & DeLeo, 2010).

The identification and detection of *S. aureus* or MRSA in the laboratory is performed by either conventional or molecular methods, both methods have their own advantages and disadvantages depending on the equipments and expertise available in the laboratory setting (Tan, 2003). More research on *S. aureus* or MRSA needs to be conducted to expedite its diagnosis and appropriate clinical management.

1.2 Problem Statement

The rise in drug virulent strains of *S. aureus* poses a challenge for clinicians to treat patients. *BlaR1* as a sensor/inducer gene play a central role in increasing resistant and limited choice of antibiotics for treatment of *S. aureus* infections in hospital setting. *BlaZ* gene detection was recommended by (CLSI, 2016). Why *blaR1* was chosen because this study embarks on the potential for *blaR1* gene detection to discriminate between β-lactam resistance and sensitivity of clinical *S. aureus* isolates. The aim of this study is to provide a confirmation of resistance to β-lactam antibiotics among clinical isolates of *S. aureus* by detecting *blaR1* gene. Laboratory detection of *blaR1* gene will confirm the resistance of *S. aureus* against β-lactam antibiotics which would be useful for clinicians to efficiently manage patients infected with phenotypic penicillin susceptible strain of *S. aureus* in the hospital.

1.3 Objectives of the Study

1.3.1 General Objective:

The general objective of this study is to detect the presence of *blaR1* gene among clinical isolates of *Staphylococcus aureus* and to determine its relationship with phenotypic antibiotic resistance of the bacteria.

1.3.2 Specific Objectives

1. To determine antimicrobial susceptibility pattern of *Staphylococcus aureus* strain isolated from Hospital Serdang from June to November 2016.
2. To detect the presence of *blaR1* gene among clinical isolates of *Staphylococcus aureus*.
3. To determine the association between the presence of *blaR1* gene with *Staphylococcus aureus* antimicrobial susceptibility pattern.
4. To detect the presence of *mec*A gene, and other bla system genes among MRSA and penicillin susceptible *Staphylococcus aureus* strains.

REFERENCES

Ahmad, N., Ruzan, I. N., Ghani, M. K. A., Hussin, A., Nawi, S., Aziz, M. N., Maning, N., & Eow, V. L. K. (2009). Characteristics of community-and hospital-acquired meticillin resistant *Staphylococcus aureus* strains carrying SCC*mec* type iv isolated in Malaysia. *Journal of Medical Microbiology*, 58(9): 1213-1218.

Al-Ruaily, M. A., & Khalil, O. M. (2011). Detection of (*mec*A) gene in methicillin resistant *Staphylococcus aureus* (MRSA) at prince a/rhman sidery hospital, al-jouf, Saudi Arabia. *Journal of Medical Genetics and Genomics*, 3(3): 41-45.

Al-Talib, H., Yean, C. Y., Al-Khateeb, A., Singh, K.-K. B., Hasan, H., Al-Jashamy, K., & Ravichandran, M. (2010). Comparative evaluation of five culture media with triplex PCR assay for detection of methicillin resistant *Staphylococcus aureus*. *Current Microbiology*, 61(1): 1-6.

Al-Talib, H. I., Yean, C. Y., Al-Jashamy, K., & Hasan, H. (2010). Methicillin-resistant *Staphylococcus aureus* nosocomial infection trends in hospital Universiti Sains Malaysia during 2002-2007. *Annals of Saudi Medicine*, 30(5): 358.

Al-Zahrani, I. A. (2011). A novel multiplex PCR-based tool of typing strains of *Staphylococcus aureus*. Newcastle University, United Kingdom.

Ammons, D. R., Puttagunta, R., Granados, J. C., de la Garza, G., Eyambe, G. S., & Rampersad, J. (2010). An exploratory study of methicillin resistant *Staphylococcus aureus* and SCC*mec* elements obtained from a community setting along the Texas border with Mexico. *Current Microbiology*, 60(5): 321-326.

Anand, K., Agrawal, P., Kumar, S., & Kapila, K. (2009). Comparison of cefoxitin disc diffusion test, oxacillin screen agar, and PCR for *mec*A gene for detection of MRSA. *Indian Journal of Medical Microbiology*, 27(1): 27.

Arora, B., & Arora, D. (2007). *Practical Microbiology*: CBS Publishers & Distributors.

Ashby, D. R., Power, A., Singh, S., Choi, P., Taube, D. H., Duncan, N. D., & Cairns, T. D. (2009). Bacteremia associated with tunneled hemodialysis catheters: Outcome after attempted salvage. *Clinical Journal of the American Society of Nephrology*, 4(10): 1601-1605.

Azis, N. M., Ab Hamid, A., Pung, H. P., Yahya, F. A., Nordin, S. A., Neela, V., Suhaili, Z., & Desa, M. N. M. (2014). *Staphylococcus aureus* infection risk in a population of health sciences students at a public University. *Iranian Journal of Public Health*, 43(3): 112.

Bell, J. M., Turnidge, J. D., & Participants, S. A. (2002). High prevalence of oxacillin-resistant *Staphylococcus aureus* isolates from hospitalized patients in asia-pacific and south africa: Results from sentry antimicrobial surveillance program, 1998-1999. *Antimicrobial Agents and Chemotherapy*, 46(3): 879-881.

Berger-Bachi, B. (1997). Resistance not mediated by beta-lactamase (methicillin resistance). *The Staphylococci in human disease. Churchill Livingstone, New York, NY*, 158-174.

Boudreau, M. A., Fishovitz, J., Llarrull, L. I., Xiao, Q., & Mobashery, S. (2015). Phosphorylation of *blar1* in manifestation of antibiotic resistance in methicillin resistant *Staphylococcus aureus* and its abrogation by small molecules. *ACS Infectious Diseases*, 1(10): 454-459.

Brown, D. F., Edwards, D. I., Hawkey, P. M., Morrison, D., Ridgway, G. L., Towner, K. J., Wren, M. W., & Chemotherapy, J. W. P. o. t. B. S. f. A. (2005). Guidelines for the laboratory diagnosis and susceptibility testing of methicillin resistant *Staphylococcus aureus* (MRSA). *Journal of Antimicrobial Chemotherapy*, 56(6): 1000-1018.

Centre for Disease Control and Prevention. (2015). Protocol for emm typing. Retrieved from http://www.cdc.gov/streplab/protocol-emm-type.html.

Chambers, H. F. (1997). Methicillin resistance in Staphylococci: Molecular and biochemical basis and clinical implications. *Clinical Microbiology Reviews*, 10(4): 781-791.

Chambers, H. F., & DeLeo, F. R. (2009). Waves of resistance: *Staphylococcus aureus* in the antibiotic era. *Nature Reviews Microbiology*, 7(9): 629-641.

Chambers, H. F., & Hackbarth, C. (1992). Methicillin resistant *staphylococcus aureus*: Genetics and mechanisms of resistance. *Methicillin resistant Staphylococcus aureus, clinical management and laboratory aspects. Marcel Dekker, Inc., New York, NY*, 21-35.

Clinical and Laboratory Standards Institute. (2016). Performance standard for antimicrobial susceptibility testing; Twenty-six edition informational suplement. Document M100-S26. Wayne, PA.

Clinical and Laboratory Standards Institute. (2011). Performance standard for antimicrobial susceptibility testing; Twenty-first edition informational suplement. Document M100-S21. Wayne, PA.

Cohen, S., & Sweeney, H. M. (1968). Constitutive penicillinase formation in *Staphylococcus aureus* owing to a mutation unlinked to the penicillinase plasmid. *Journal of Bacteriology*, 95(4): 1368-1374.

Control, C. f. D., & Prevention. (2002). *Staphylococcus aureus* resistant to vancomycin United States, 2002. *MMWR. Morbidity and Mortality Weekly Report*, 51(26): 565.

Cosgrove, S. E., Sakoulas, G., Perencevich, E. N., Schwaber, M. J., Karchmer, A. W., & Carmeli, Y. (2003). Comparison of mortality associated with methicillin resistant and methicillin susceptible *Staphylococcus aureus* bacteremia: A meta-analysis. *Clinical Infectious Diseases*, 36(1): 53-59.

David Greenwood, John Peutherer, Richard Slack, & Peutherer, J. F. (2002). Medical microbiology: A guide to microbial infections - pathogenesis, immunity, laboratory diagnosis and control / edition 16. *Elsevier Health Sciences*, 168-173.

De Lencastre, H., Oliveira, D., & Tomasz, A. (2007). Antibiotic resistant *Staphylococcus aureus*: A paradigm of adaptive power. *Current Opinion in Microbiology*, 10(5): 428-435.

De Sousa, M. A. (2004). Bridges from hospitals to the laboratory: Genetic portraits of methicillin resistant *Staphylococcus aureus* clones. *FEMS Immunology & Medical Microbiology*, 40(2): 101-111.

Dinges, M. M., Orwin, P. M., & Schlievert, P. M. (2000). Exotoxins of *Staphylococcus aureus*. *Clinical Microbiology Reviews*, 13(1): 16-34.

Falagas, M. E., & Vardakas, K. Z. (2008). Benefit-risk assessment of linezolid for serious gram-positive bacterial infections. *Drug Safety*, 31(9): 753-768.

Fluit, A. C., & Schmitz, F.-J. (2003). *MRSA: Current perspectives*: Horizon Scientific Press.

Fluit, A. C., Visser, M. R., & Schmitz, F.-J. (2001). Molecular detection of antimicrobial resistance. *Clinical Microbiology Reviews*, 14(4): 836-871.

Foster, T. J. (2005). Immune evasion by Staphylococci. *Nature Reviews Microbiology*, 3(12): 948-958.

Foster, T. J., & Höök, M. (1998). Surface protein adhesins of *Staphylococcus aureus. Trends in Microbiology*, 6(12): 484-488.

Fuda, C., Fisher, J., & Mobashery, S. (2005). B-lactam resistance in *Staphylococcus aureus*: The adaptive resistance of a plastic genome. *Cellular and Molecular Life Sciences*, 62(22): 2617-2633.

Garrity, G. M., Bell, J. A., & Lilburn, T. G. (2004). Taxonomic outline of the prokaryotes. Bergey's manual of systematic bacteriology. *Springer, New York, Berlin, Heidelberg*.

Ghaznavi-Rad, E., Shamsudin, M. N., Sekawi, Z., van Belkum, A., & Neela, V. (2010). A simplified multiplex PCR assay for fast and easy discrimination of globally distributed Staphylococcal cassette chromosome *mec* types in meticillin resistant *Staphylococcus aureus*. *Journal of Medical Microbiology,* 59(10): 1135-1139.

Gordon, R. J., & Lowy, F. D. (2008). Pathogenesis of methicillin resistant *Staphylococcus aureus* infection. *Clinical Infectious Diseases,* 46(Supplement 5): S350-S359.

Greenwood, D., Finch, R., Davey, P., & Wilcox, M. (2007). *Antimicrobial chemotherapy*: Oxford university press, USA.

Grundmann, H., Aires-de-Sousa, M., Boyce, J., & Tiemersma, E. (2006). Emergence and resurgence of meticillin resistant *Staphylococcus aureus* as a public-health threat. *The Lancet,* 368(9538): 874-885.

Hackbarth, C. J., & Chambers, H. F. (1993). *BlaI* and *blaR1* regulate beta-lactamase and PBP2a production in methicillin resistant *Staphylococcus aureus. Antimicrobial Agents and Chemotherapy,* 37(5): 1144-1149.

Hill, R. L., Kearns, A. M., Nash, J., North, S. E., Pike, R., Newson, T., Woodford, N., Calver, R., & Livermore, D. M. (2010). Linezolid-resistant st36 methicillin resistant *Staphylococcus aureus* associated with prolonged linezolid treatment in two paediatric cystic fibrosis patients. *Journal of Antimicrobial Chemotherapy,* 65(3): 442-445.

Hiramatsu, K., Aritaka, N., Hanaki, H., Kawasaki, S., Hosoda, Y., Hori, S., Fukuchi, Y., & Kobayashi, I. (1997). Dissemination in Japanese hospitals of strains of *Staphylococcus aureus* heterogeneously resistant to vancomycin. *The Lancet,* 350(9092): 1670-1673.

Holden, M. T., Feil, E. J., Lindsay, J. A., Peacock, S. J., Day, N. P., Enright, M. C., Foster, T. J., Moore, C. E., Hurst, L., & Atkin, R. (2004). Complete genomes of two clinical *Staphylococcus aureus* strains: Evidence for the rapid evolution of virulence and drug resistance. *Proceedings of the National Academy of Sciences of the United States of America,* 101(26): 9786-9791.

Holmes, A., Ganner, M., McGuane, S., Pitt, T., Cookson, B., & Kearns, A. (2005). *Staphylococcus aureus* isolates carrying panton-valentine leucocidin genes in england and wales: Frequency, characterization, and association with clinical disease. *Journal of Clinical Microbiology*, 43(5): 2384-2390.

Hou, Z., Zhou, Y., Wang, H., Bai, H., Meng, J., Xue, X., & Luo, X. (2011). Co-blockade of *mecR1*/*blaR1* signal pathway to restore antibiotic susceptibility in clinical isolates of methicillin resistant *Staphylococcus aureus. Archives of Medical Science,* 7(3): 414-422.

Jain, A., Agarwal, A., & Verma, R. K. (2008). Cefoxitin disc diffusion test for detection of meticillin resistant Staphylococci. *Journal of Medical Microbiology*, 57(8): 957-961.

Johnson, A. (1998). Antibiotic resistance among clinically important gram-positive bacteria in the UK. *Journal of Hospital Infection*, 40(1): 17-26.

Johnson, A. P., Pearson, A., & Duckworth, G. (2005). Surveillance and epidemiology of MRSA bacteraemia in the uk. *Journal of Antimicrobial Chemotherapy*, 56(3): 455-462.

Kaneko, J., & Kamio, Y. (2004). Bacterial two-component and hetero-heptameric pore-forming cytolytic toxins: Structures, pore-forming mechanism, and organization of the genes. *Bioscience, Biotechnology, and Biochemistry*, 68(5): 981-1003.

Katayama, Y., Ito, T., & Hiramatsu, K. (2000). A new class of genetic element, Staphylococcus cassette chromosome *mec*, encodes methicillin resistance in *Staphylococcus aureus*. *Antimicrobial Agents and Chemotherapy*, 44(6): 1549-1555.

Kernodle, D. (2000). Mechanisms of resistance to β-lactam antibiotics. *Gram-Positive Pathogens*, 769-781.

Klein, E., Smith, D. L., & Laxminarayan, R. (2007). Hospitalizations and deaths caused by methicillin resistant *Staphylococcus aureus*, United States, 1999-2005. *Emerging Infectious Diseases*, 13(12): 1840.

Kowalski, T. J., Berbari, E. F., & Osmon, D. R. (2005). Epidemiology, treatment, and prevention of community-acquired methicillin resistant *Staphylococcus aureus* infections. Paper presented at the Mayo Clinic Proceedings.

Kwok, A. Y., & Chow, A. W. (2003). Phylogenetic study of Staphylococcus and macrococcus species based on partial hsp60 gene sequences. *International Journal of Systematic and Evolutionary Microbiology*, 53(1): 87-92.

Lindsay, J. A., & Holden, M. T. (2004). *Staphylococcus aureus*: Superbug, super genome? *Trends in Microbiology*, 12(8): 378-385.

Llarrull, L. I., Prorok, M., & Mobashery, S. (2010). Binding of the gene repressor *blaI* to the bla operon in methicillin resistant *Staphylococcus aureus. Biochemistry*, 49(37): 7975-7977.

Lowy, F. D. (2003). Antimicrobial resistance: The example of *Staphylococcus aureus. The Journal of Clinical Investigation*, 111(9): 1265-1273.

Malachowa, N., & DeLeo, F. R. (2010). Mobile genetic elements of *Staphylococcus aureus. Cellular and Molecular Life Sciences*, 67(18): 3057-3071.

McCallum, N., Berger-Bächi, B., & Senn, M. M. (2010). Regulation of antibiotic resistance in *Staphylococcus aureus. International Journal of Medical Microbiology,* 300(2): 118-129.

McClure, J.-A., Conly, J. M., Lau, V., Elsayed, S., Louie, T., Hutchins, W., & Zhang, K. (2006). Novel multiplex PCR assay for detection of the Staphylococcal virulence marker panton-valentine leukocidin genes and simultaneous discrimination of methicillin susceptible from resistant Staphylococci. *Journal of Clinical Microbiology,* 44(3): 1141-1144.

McCormick, J. K., Yarwood, J. M., & Schlievert, P. M. (2001). Toxic shock syndrome and bacterial superantigens: An update. *Annual Reviews in Microbiology,* 55(1): 77-104.

Melzer, M., Eykyn, S., Gransden, W., & Chinn, S. (2003). Is methicillin resistant *Staphylococcus aureus* more virulent than methicillin susceptible *S. aureus*? A comparative cohort study of British patients with nosocomial infection and bacteremia. *Clinical Infectious Diseases,* 37(11): 1453-1460.

Mohammadi, S., Sekawi, Z., Monjezi, A., Maleki, M.-H., Soroush, S., Sadeghifard, N., Pakzad, I., Azizi-Jalilian, F., Emaneini, M., & Asadollahi, K. (2014). Emergence of SCC*mec* type iii with variable antimicrobial resistance profiles and spa types among methicillin resistant *Staphylococcus aureus* isolated from healthcare and community acquired infections in the west of Iran. *International Journal of Infectious Diseases,* 25: 152-158.

Morales, G., Picazo, J. J., Baos, E., Candel, F. J., Arribi, A., Peláez, B., Andrade, R., de la Torre, M.-Á., Fereres, J., & Sánchez-García, M. (2010). Resistance to linezolid is mediated by the cfr gene in the first report of an outbreak of linezolid resistant *Staphylococcus aureus. Clinical Infectious Diseases,* 50(6): 821-825.

Moreillon, P. (2008). New and emerging treatment of *Staphylococcus aureus* infections in the hospital setting. *Clinical Microbiology and Infection,* 14(s3): 32-41.

Morin, R. B., & Gorman, M. (2014). *The biology of β-lactam antibiotics*: Elsevier.

Neela, V., Moghaddam, H. G., van Belkum, A., Horst-Kreft, D., Mariana, N. S., & Rad, E. G. (2010). First report on methicillin resistant *Staphylococcus aureus* of Spa type T037, Sequence Type 239, SCC*mec* type III/IIIA in Malaysia. *European Journal of Clinical Microbiology and Infectious Diseases,* 29(1): 115-117.

Novick, R. (2006). Staphylococcal pathogenesis and pathogenicity factors: Genetics and regulation. *Gram-Positive Pathogens,* 2: 496.

NSAR. (2014). National surveillance on antibiotic resistance. *National surveillance on antibiotic resistance: Report for 2014.* Malaysia: Ministry of health Malaysia; 2014.

NSAR. (2015). National surveillance on antibiotic resistance. *National surveillance on antibiotic resistance: Report for 2015.* Malaysia: Ministry of Health Malaysia; 2015.

Oliveira, D. C., & De Lencastre, H. (2011). Methicillin resistance in *Staphylococcus aureus* is not affected by the overexpression in trans of the *mec*A gene repressor: A surprising observation. *PLoS ONE,* 6(8): e23287.

Paintsil, E. (2007). Pediatric community-acquired methicillin resistant *Staphylococcus aureus* infection and colonization: Trends and management. *Current Opinion in Pediatrics,* 19(1): 75-82.

Palavecino, E. (2007). Clinical, epidemiological, and laboratory aspects of methicillin resistant *Staphylococcus aureus* (MRSA) infections. *Methicillin-Resistant Staphylococcus aureus (MRSA) Protocols*, 1-19.

Pence, M. A., Haste, N. M., Meharena, H. S., Olson, J., Gallo, R. L., Nizet, V., & Kristian, S. A. (2015). Beta-lactamase repressor *blaI* modulates *Staphylococcus aureus* cathelicidin antimicrobial peptide resistance and virulence. *PLoS ONE,* 10(8): e0136605.

Pereira, L. A., Harnett, G. B., Hodge, M. M., Cattell, J. A., & Speers, D. J. (2014). Real-time PCR assay for detection of *blaZ* genes in *Staphylococcus aureus* clinical isolates. *Journal of Clinical Microbiology,* 52(4): 1259-1261.

Pozo, J., & Patel, R. (2007). The challenge of treating biofilm-associated bacterial infections. *Clinical Pharmacology & Therapeutics,* 82(2): 204-209.

Pulingam, T., Ibrahim, P., & Toh, S.-M. (2014). Investigation of linezolid resistance among methicillin resistant *Staphylococcus aureus* strains isolated from state hospitals in the East and West coast of Malaysia. *Malaysian Journal of Microbiology*, 10(2): 101-105.

Richter, S., Doern, G., Heilmann, K., Miner, S., Tendolkar, S., Riahi, F., & Diekema, D. (2016). Detection and prevalence of penicillin-susceptible *Staphylococcus aureus* in the United States in 2013. *Journal of Clinical Microbiology*, 54(3): 812-814.

Rohani, M., Raudzah, A., Lau, M., Zaidatul, A., Salbiah, M., Keah, K., Noraini, A., & Zainuldin, T. (2000). Susceptibility pattern of *Staphylococcus aureus* isolated in Malaysian hospitals. *International Journal of Antimicrobial Agents,* 13(3): 209-213.

Rohani, M., Zainuldin, M., Koay, A., & Lau, M. (1999). Antibiotec resistance patterns of bacteria isolated in Malaysian hospitals. *International Medical Journal-Tokyo,* 6: 47-52.

Rozgonyi, F., Kocsis, E., Kristof, K., & Nagy, K. (2007). Is MRSA more virulent than MSSA? *Clinical Microbiology and Infection,* 13(9): 843-845.

Ryan, K. J., & Ray, C. G. (2004). *Medical Microbiology*: McGraw Hill.

Sabet, N. S., Subramaniam, G., Navaratnam, P., & Sekaran, S. D. (2007). Detection of *mec*A and *erm*A genes and simultaneous identification of *Staphylococcus aureus* using triplex real-time PCR from Malaysian *S. aureus* strain collections. *International Journal of Antimicrobial Agents,* 29(5): 582-585.

Safo, M. K., Zhao, Q., Ko, T.-P., Musayev, F. N., Robinson, H., Scarsdale, N., Wang, A. H.-J., & Archer, G. L. (2005). Crystal structures of the *blaI* repressor from *Staphylococcus aureus* and its complex with DNA: Insights into transcriptional regulation of the bla and mec operons. *Journal of Bacteriology,* 187(5): 1833-1844.

Saiful, A., Mastura, M., Zarizal, S., Mazurah, M., Shuhaimi, M., & Ali, A. (2006). Detection of methicillin resistant *Staphylococcus aureus* using *mec*A/nuc genes and antibiotic susceptibility profile of Malaysian clinical isolates. *World Journal of Microbiology and Biotechnology,* 22(12): 1289-1294.

Schmitz, F.-J., & Jones, M. E. (1997). Antibiotics for treatment of infections caused by MRSA and elimination of MRSA carriage. What are the choices? *International Journal of Antimicrobial Agents,* 9(1): 1-19.

Schneider-Lindner, V., Brassard, P., & Suissa, S. (2008). Mortality after infection with methicillin resistant *Staphylococcus aureus* (MRSA) diagnosed in the community. *BMC Medicine,* 6(1): 2.

Shands, K. N., Schmid, G. P., Dan, B. B., Blum, D., Guidotti, R. J., Hargrett, N. T., Anderson, R. L., Hill, D. L., Broome, C. V., & Band, J. D. (1980). Toxic-shock syndrome in menstruating women: Association with tampon use and *Staphylococcus aureus* and clinical features in 52 cases. *New England Journal of Medicine,* 303(25): 1436-1442.

Shittu, A. O., Udo, E. E., & Lin, J. (2007). Insights on virulence and antibiotic resistance: A review of the accessory genome of *Staphylococcus aureus*. *Wounds,* 19(9): 237.

Sieradzki, K., Roberts, R. B., Haber, S. W., & Tomasz, A. (1999). The development of vancomycin resistance in a patient with methicillin resistant *Staphylococcus aureus* infection. *New England Journal of Medicine,* 340(7): 517-523.

Stenz, L. (2011). The GTP-dependant pleiotropic repressor" codY" regulates biofilm formation in *Staphylococcus aureus.* University of Geneva.

Strommenger, B., Kettlitz, C., Werner, G., & Witte, W. (2003). Multiplex PCR assay for simultaneous detection of nine clinically relevant antibiotic resistance genes in *Staphylococcus aureus*. *Journal of Clinical Microbiology,* 41(9): 4089-4094.

System, N. N. I. S. (2004). National nosocomial infections surveillance (NNIS) system report, data summary from January 1992 through June 2004, issued October 2004. *American Journal of Infection Control,* 32(8): 470.

Takata, T., Shirakawa, T., Ito, J., Okamoto, A., Massi, M. N., Kinoshita, S., Hatta, M., & Kawabata, M. (2006). SCC*mec* typing and detection of VISA-related genes in methicillin resistant *Staphylococcus aureus* clinical strains from Kobe University Hospital, Japan. *The Southeast Asian Journal of Tropical Medicine and Public Health,* 37(6): 1149-55.

Tan, T. Y. (2003). Use of molecular techniques for the detection of antibiotic resistance in bacteria. *Expert Review of Molecular Diagnostics,* 3(1): 93-103.

Tang, S. S., Apisarnthanarak, A., & Hsu, L. Y. (2014). Mechanisms of β-lactam antimicrobial resistance and epidemiology of major community-and healthcare-associated multidrug-resistant bacteria. *Advanced Drug Delivery Reviews,* 78: 3-13.

Tasara, T., Cernela, N., & Stephan, R. (2013). Function impairing mutations in *blaZ* and *blaR* genes of penicillin susceptible *Staphylococcus aureus* strains isolated from bovine mastitis. *Schweiz. Arch. Tierheilkd,* 155: 359-363.

Thumanu, K., Cha, J., Fisher, J. F., Perrins, R., Mobashery, S., & Wharton, C. (2006). Discrete steps in sensing of β-lactam antibiotics by the *blaR1* protein of the methicillin resistant *Staphylococcus aureus* bacterium. *Proceedings of the National Academy of Sciences,* 103(28): 10630-10635.

Tiwari, H. K., & Sen, M. R. (2006). Emergence of vancomycin resistant *Staphylococcus aureus* (VRSA) from a tertiary care hospital from northern part of India. *BMC Infectious Diseases,* 6(1): 156.

Todar, K. (2008). *Todar's online textbook of bacteriology*.

Todd, J., Fishaut, M., Kapral, F., & Welch, T. (1978). Toxic-shock syndrome associated with phage-group-i Staphylococci. *The Lancet,* 312(8100): 1116-1118.

Tong, S. Y., Davis, J. S., Eichenberger, E., Holland, T. L., & Fowler, V. G. (2015). *Staphylococcus aureus* infections: Epidemiology, pathophysiology, clinical manifestations, and management. *Clinical Microbiology Reviews,* 28(3): 603-661.

Trindade, P. d. A., Pacheco, R. L., Costa, S. F., Rossi, F., Barone, A. A., Mamizuka, E. M., & Levin, A. S. (2005). Prevalence of SCC*mec* type iv in nosocomial bloodstream isolates of methicillin resistant *Staphylococcus aureus. Journal of Clinical Microbiology,* 43(7): 3435-3437.

Vandenesch, F., Naimi, T., Enright, M. C., Lina, G., Nimmo, G. R., Heffernan, H., Liassine, N., Bes, M., Greenland, T., & Reverdy, M.-E. (2003). Community-acquired methicillin resistant *Staphylococcus aureus* carrying panton-valentine leukocidin genes: Worldwide emergence. *Emerging Infectious Diseases,* 9(8): 978-984.

Vesterholm-Nielsen, M., Olhom, L. M., Elmerdahl, O. J., & Moller, A. F. (1998). Occurrence of the *blaZ* gene in penicillin resistant *Staphylococcus aureus* isolated from bovine mastitis in Denmark. *Acta Veterinaria Scandinavica,* 40(3): 279-286.

Vourli, S., Vagiakou, H., Ganteris, G., Orfanidou, M., Polemis, M., Vatopoulos, A., & Malamou-Ladas, H. (2007). High rates of community-acquired, panton-valentine leukocidin (PVL)-positive methicillin resistant *S. aureus* (MRSA) infections in adult outpatients in Greece. *Euro Surveill,* 14(2).

Wang, G., Hindler, J. F., Ward, K. W., & Bruckner, D. A. (2006). Increased vancomycin MICs for *Staphylococcus aureus* clinical isolates from a University hospital during a 5-year period. *Journal of Clinical Microbiology,* 44(11): 3883-3886.

Wang, L., & Barrett, J. F. (2007). Control and prevention of MRSA infections. *Methicillin-Resistant Staphylococcus aureus (MRSA) Protocols,* 209-225.

Weigel, L. M., Donlan, R. M., Shin, D. H., Jensen, B., Clark, N. C., McDougal, L. K., Zhu, W., Musser, K. A., Thompson, J., & Kohlerschmidt, D. (2007). High-level vancomycin resistant *Staphylococcus aureus* isolates associated with a polymicrobial biofilm. *Antimicrobial Agents and Chemotherapy,* 51(1): 231-238.

Wieland, B., Feil, C., Gloria-Maercker, E., Thumm, G., Lechner, M., Bravo, J.-M., Poralla, K., & Götz, F. (1994). Genetic and biochemical analyses of the biosynthesis of the yellow carotenoid 4, 4'-diaponeurosporene of *Staphylococcus aureus*. *Journal of Bacteriology,* 176(24): 7719-7726.

Wright III, J. S., & Novick, R. P. (2003). Virulence mechanisms in MRSA pathogenesis. *MRSA Current Perspectives,* 213-251.

Xu, S. X., & McCormick, J. K. (2012). Staphylococcal superantigens in colonization and disease. *Frontiers in Cellular and Infection Microbiology, 2*.

Yang, F., Wang, Q., Wang, X.-r., Wang, L., LI, X.-p., Luo, J.-y., Zhang, S.-d., & LI, H.-s. (2016). Genetic characterization of antimicrobial resistance in *Staphylococcus aureus* isolated from bovine mastitis cases in northwest China. *Journal of Integrative Ariculture*, 15: 2842-2847.

Yoshida, K., Shoji, H., Hanaki, H., Yanagisawa, C., Ikeda-Dantsuji, Y., Fukuchi, K., Adachi, M., & Niki, Y. (2009). Linezolid-resistant methicillin-resistant Staphylococcus aureus isolated after long-term, repeated use of linezolid. *Journal of Infection and Chemotherapy*, 15(6): 417-419.

Zong, Z., Peng, C., & Lü, X. (2011). Diversity of SCC*mec* elements in methicillin resistant coagulase-negative Staphylococci clinical isolates. *PloS ONE*, 6(5): e20191.