ZULFAQAR Journal of Defence Science, Engineering & Technology
e-ISSN: 2773-5281
Vol. 4, Issue 2 (2021)
DOI: https://doi.org/10.58247/jdset-2021-0402-13
Journal homepage: https://zulfaqarjdset.upnm.edu.my

ANTIBIOTIC SUSCEPTIBILITY PROFILES OF STAPHYLOCOCCUS AUREUS IN HOSPITAL ANGKATAN TENTERA TUANKU MIZAN (HATTM), MALAYSIA: A PRELIMINARY STUDY

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ARTICLE INFO

ARTICLE HISTORY
Received: 14-07-2021
Revised: 08-09-2021
Accepted: 10-10-2021
Published: 31-12-2021

KEYWORDS
Antibiotic susceptibility profiles
Methicillin-resistant S aureus (MRSA)
Methicillin-sensitive S aureus (MSSA)
Staphylococcus aureus

ABSTRACT

Staphylococcus aureus is a human pathogen causing a variety of diseases ranging from superficial skin and soft-tissue infections to life-threatening infections. Nowadays, the treatment has become complicated due to the emergence of methicillin-resistant S. aureus (MRSA). It is an established pathogen that causes hospital- and community-acquired infections worldwide. This study was a preliminary retrospective study involving S. aureus clinical isolates from Hospital Angkatan Tentera Tuanku Mizan (HATTM) for a period of 6 months (October 2018 until March 2019). The study was conducted to determine the S. aureus antibiotic susceptibility profiles and its association with types of infection, gender, wards, age of patients and types of specimens. Standard bacteriological method was used for S. aureus isolation from various clinical specimens including blood, urine, pus and wound, eye, throat, nasal, pericardial fluid, tracheal aspirate, high vagina swab (HVS), bronchial alveolar lavage (BAL) and tissue. Kirby-Bauer disc diffusion method was utilized for antibiotic susceptibility profiles determination. Ninety-five S. aureus strains were isolated from 3571 specimens. Twenty-six of the isolates (27%) was identified as MRSA and 69 (73%) was identified as methicillin-sensitive S. aureus (MSSA). Among the MRSA, 4 isolates were hospital-acquired MRSA (HA-MRSA) and the rest were community-acquired MRSA (CA-MRSA). There was a statistically significant association between isolation of MRSA with age of patient as well as types of infection or origin of the MRSA ($p<0.05$). Only 42 (44.2%) of the S. aureus isolates were fully susceptible to all antibiotics. Almost half isolates (n=46, 48.4%) were resistant to at least two antibiotics and seven (7.4%) isolates were resistant to one type of antibiotic only. None of the isolate showed reduced susceptibility nor resistant to vancomycin. Future study with a larger sample size using a wider study period needs to be done to confirm that vancomycin-resistant S. aureus has not yet been established in HATTM.

1.0 INTRODUCTION

Staphylococcus aureus is a Gram-positive bacterium that causes a variety of diseases ranging from superficial skin and soft-tissue infections to life-threatening infections such as infective endocarditis and toxic shock syndrome [1-2]. Methicillin-resistant *S. aureus* (MRSA) is extensively recognized as one of the common pathogens causing hospital- and community- acquired infections. The MRSA is developed from methicillin-susceptible *S. aureus* (MSSA) via acquisition of Staphylococcal cassette chromosome mec

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(SCCmec) which carries *mecA* gene. The gene encodes the penicillin-binding protein (PBP2a) that confers resistance to all β-lactam antibiotics [3].

Globally, the emergence of MRSA strains which are also multi-drug resistant, have posed significant threat to the public health [1, 4]. It has been reported that MRSA infections tend to prolong the length of hospital stay, involve higher cost and are associated with a high rate of mortality [5-7]. There are two types of MRSA based on the origin of the isolates, known as hospital-acquired MRSA (HA-MRSA) and community-acquired MRSA (CA-MRSA) [7]. There are enormous struggles in the treatment and prevention of MRSA infections in hospital due to the limited treatment options. Vancomycin has been the drug of choice in the treatment of the infections [4]. However, reports regarding the emergence of MRSA isolates that have reduced susceptibility to this drug were published in many parts of the world due to its extensive usage [3, 8-9]. The isolates are known as vancomycin-intermediate resistant *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA). There is no documented report yet on emergence of VRSA in Malaysia. Unfortunately, a case of VRSA was reported in Indonesia, which is the neighbouring country of Malaysia
[7, 10].

It has been reported that the *S. aureus* antibiotic susceptibility profiles may vary from region to region [7, 11]. The prevalence rate of MRSA infections is increasing in hospitals worldwide with high rates (>50%) reported in Asia, Malta and South America [12-13]. In Malaysia, the prevalence of MRSA among *S. aureus* isolates ranged from 17% to 35.5% [7, 13]. Recent Malaysian National Surveillance of Antimicrobial Resistance (NSAR) annual report that included antibiotic susceptibility profiles from the Ministry of Health and universities teaching hospitals in Malaysia revealed that there was an increment of MRSA rate in year 2017 (19.8%) compared to the previous year 2016 (18.0%) [14]. Meanwhile, the incidence of CA-MRSA infection has been widely reported among healthy adults, soldiers, pregnant women, prisoners and children [15-17].

There are limited studies involving clinical *S. aureus* isolates from Malaysian hospitals to monitor the trends of *S. aureus* infections and antibiotic susceptibility profiles. Thus, this study was conducted to establish a preliminary data on Hospital Angkatan Tentera Tuanku Mizan (HATTM) *S. aureus* antibiotic susceptibility profiles and to describe its association with types of infection, gender, ward/department, age of patients and types of specimens. The data is important to provide new insight into the infection control particularly in the military hospital environment in Malaysia.

2.0 MATERIALS AND METHODS

2.1 Bacterial Strains

Staphylococcus aureus isolated from 3571 processed specimens between months of October 2018 to March 2019 from Department of Pathology, Hospital Angkatan Tentera Tuanku Mizan (HATTM) were analysed in this study. Strains were obtained from various clinical specimens including blood, urine, pus and wound, eye, throat, nasal, pericardial fluid, tracheal aspirate, high vagina swab (HVS), bronchial alveolar lavage (BAL) and tissue. The specimens were collected from wards such as orthopaedic, paediatric, surgical, medical, obstetrics and gynaecology (O&G), outpatient department (OPD), intensive care unit (ICU) and neonatal ICU (NICU). Standard bacteriological methods were used for isolation and identification of the strains from the specimens. Initial *S. aureus* screening was done based on the presence of yellow colonies with bright yellow zone on blood agar. The colonies were further identified by Gram-stain, catalase test as well as phenotypic confirmation using coagulase test. *Staphylococcus aureus* ATCC 25923 was used as positive control for phenotypic identification.

2.2 Antibiotic Susceptibility Test (AST)

Antibiotic Susceptibility Test (AST) was done on Muller Hinton Agar (Oxoid, UK) using the Kirby-Bauer's disc diffusion method as described by Clinical Laboratory Standard Institute (CLSI, 2018). Standard antibiotic discs were used (Oxoid, UK). Methicillin resistance was detected using cefoxitin (30 µg) disc. Isolates with inhibition zone diameter ≤ 21 mm around the disc were considered as MRSA strains. Susceptibility tests to ampicillin (10 µg), cefepime (30 µg), azythromycin (15 µg), cefoperazone (75 µg), cefuroxime (30 µg), clindamycin (2 µg), erythromycin (15 µg), gentamycin (10 µg), linezolid (30 µg), novobiocin (30 µg), fusidic Acid (10 µg), rifampicin (5 ug), penicillin (10 µg) and vancomycin (30 ug)

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were also conducted. The zone sizes were measured and interpreted according to CLSI. *Staphylococcus aureus* ATCC 25923 was used as Quality Control strain.

2.3 Data Collection

This study was a retrospective study and did not involve human subjects, only bacterial strains were collected. Some demographic data associated with the *S. aureus* isolates (age, gender, ward, specimen type and history of admission) were retrieved from the hospital's medical record unit. The MRSA infection was defined as hospital acquired- (HA-) or community acquired-(CA-) MRSA based upon the data collected from the medical record and from the HATTM Infection Control Department's database. Based on the Centres for Disease Control and Prevention (CDC) [13, 18], the HA-MRSA is defined as positive culture obtained more than 48 hours after hospital admission, or history of previous hospitalization or medical procedures. Meanwhile, the CA-MRSA refers to cases with positive culture obtained less than 48 hours of admission in the absence of healthcare-associated risk factors [7, 13, 19].

2.4 Data Analysis

All collected data were analysed using the latest version of Statistical Product and Service Solutions (SPSS) software. The Chi-square test and descriptive statistical data analysis parameters were used. Statistical value $p<0.05$ was considered as significant.

2.5 Research And Ethics Approval

This study was approved by UPNM Research and Ethics Committee with approval certificate number UPNM/JKEP13/2020.

3.0 RESULTS

A total of 95 *S. aureus* isolates were obtained from the clinical specimens. The distributions of isolates based on types of MRSA, age of patients, gender, wards and types of specimens are shown in Table 1. The median age of patient was 56 years ranging from 40 days to 96 years. Majority of the *S. aureus* isolates belonged to the age group of 51 to 60 years old (n=38). Sixty-five (68.4%) isolates were collected from male patients and 30 (31.6%) isolates were from female patients. Pus and wound specimens contributed the highest number of *S. aureus* isolates (n=37/39%) followed by blood (n=36/38%), urine (n=7/7.4%), tissue (n=7/7.4%), high vagina swab (HVS) (n=2/2.2%), trachea aspirate (n=1/1%), pericardial fluid (n=1/1%), throat (n=1/1%), bronchial alveolar lavage (BAL) (n=1/1%), nasal (n=1/1%) and eye (n=1/1%).

Based on the susceptibility of isolates to cefoxitin and oxacillin, 27% (n=26) of the isolates were found to be MRSA with 20 isolates being multidrug resistant (MDR) or isolates that resistant to two and more antibiotics. Seventy-three percent (n=69) of isolates were MSSA. Fig. 1 shows the antibiotic susceptibility profiles of *S. aureus* isolates to all tested antibiotics. Only 44% (n=42) isolates were fully susceptible to all antibiotics. However, all isolates were sensitive to linezolid, novobiocin and vancomycin. The lowest frequency of susceptibility was observed to cefuroxime and fusidic acid (n=65 respectively). In comparison to MSSA, the MRSA strains have higher frequency of resistance to many antibiotics. All MRSA isolates (n=26) were resistant to ampicillin, unasyn, cefoxitin, cefuroxime, oxacillin and penicillin as shown in Fig. 2. As for other antibiotics, 58% (n=15) were resistant to azithromycin, 77% (n=20) to cefoperazone, 26.9% (n=7) to clindamycin, 50% (n=13) to erythromycin, 65% (n=17) to fusidic acid, 23% (n=6) to gentamicin and 19.2% (n=5) were resistant to rifampicin. Among the MSSA isolates, most isolates were resistant to fusidic acid (n=13) followed by azithromycin (n=12), erythromycin (n=12), gentamicin (n=7), cefuroxime (n=4), penicillin (n=3), ampicillin (n=3) and clindamycin (n=1) as shown in Fig. 3. All MSSA isolates (n=69) were susceptible to the remaining tested antibiotics.

As shown in Table 1, the MRSA infections increased significantly in the age of group > 50 years old. Most of the MRSA isolates were from patients in the age group of 51 to 60 years old (n=17) and were mostly from male patients (n=22). The mean age of patients with MRSA is 57 years old and for MSSA is 50 years old. Based on the types of infection according to the definition by CDC, most of the MRSA isolates were CA-MRSA (n=22) and the rest were HA-MRSA (n=4). The HA-MRSA isolates were isolated from pus and wound specimen (n=3) and blood specimen (n=1). Two of the HA-MRSA isolates were from patients

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in orthopaedic ward and the rest were from patients in ICU ward and medical ward. As for CA-MRSA, majority were from medical ward (n=13) followed by orthopaedic ward (n=4), ICU (n=2), surgical ward (n=2) and OPD (n=1). All HA-MRSA and CA-MRSA isolates were multidrug resistant.

The highest frequency of MRSA isolation was observed from medical ward (n=14), followed by orthopaedic ward (n=6), ICU (n=3), surgical ward (n=2) and OPD (n=1). As for MSSA, most of them were from medical ward (n=24) followed by orthopaedic ward (n=13), OPD (n=13), surgical ward (n=9), ICU (n=4), NICU (n=3), paediatric (n=2) and O&G (n=1). The highest number of MRSA isolates was from blood specimen (n=12) followed by pus and wound specimens (n=8), tissue (n=3), urine (n=1), throat (n=1) and nasal (n=1). There is a statistically significant association between MRSA isolation and age group of patients as well as types of infection ($p < 0.05$) (Table 1 and Table 2).

Table 1. Distribution of isolates based on age of patients, gender, types of MRSA infection, ward/ department and types of specimens

Distribution		MSSA	MRSA	Total
Age	<11	4	0	4
	11-20	4	0	4
	21-30	6	1	7
	31-40	8	0	8
	41-50	4	0	4
	51-60	21	17	38
	>60	22	8	30
Gender	Male	43	22	65
	Female	26	4	30
Types of MRSA	HA-MRSA	0	4	4
Infection	CA-MRSA	69	22	91
Ward/	Orthopaedic	13	6	19
Department	Medical	24	13	38
	Surgical	9	2	9
	ICU	4	3	7
	NICU	3	0	3
	OPD (Specialist Clinics)	13	1	14
	Paediatric	2	0	2
	O&G	1	0	1
Specimen	Blood	24	12	36
	HVS	2	0	2
	Urine	6	1	7
	Pus & wound	29	8	37
	Tissue	4	3	7
	Tracheal aspirate	1	0	1
	Pericardial fluid	1	0	1
	Throat	0	1	1
	BAL	1	0	1
	Nasal	0	1	1
	Eye	1	0	1

HVS: High vagina swab, BAL: Bronchial alveolar lavage, HAI: Hospital acquired infection, CAI: Community acquired infection. ICU: Intensive Care Unit, NICU: Neonatal Intensive Care Unit, OPD: Out Patient Department, O&G: Obstetrics & Gynaecology

Table 2. Results of chi-square test for association between MRSA isolation and age group of patients as well as types of infection

	X^2, df	p = value
Age groups	17.239, 6	0.008
Types of infection (CA-MRSA & HA-MRSA)	11.692, 1	0.004

Statistical value $p<0.05$ was considered as significant

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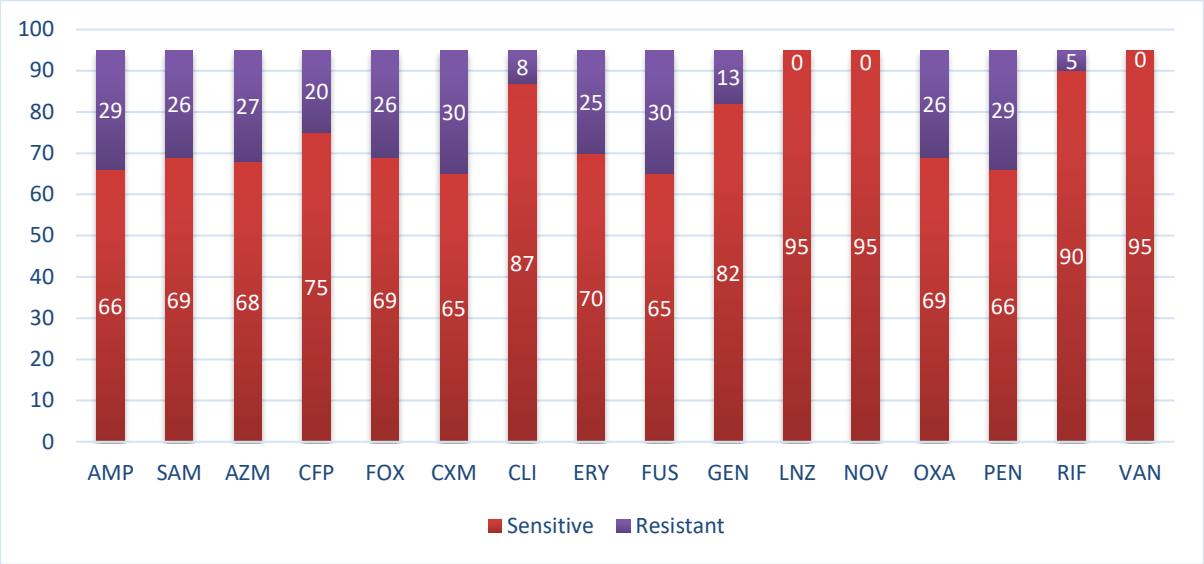

Fig. 1. Proportion of *Staphylococcus aureus* isolates antibiotic susceptibility profiles (N=95)
(AM: Ampicillin, SAM: Unasyn, AZM: Azithromycin, CFP: Cefoperazone, FOX: Cefoxitin, CXM: Cefuroxime, CLI: Clindamycin, ERY: Erythromycin, FUS: Fusidic acid, GEN: Gentamicin, LNZ: Linezolid, NOV: Novobiocin, OXA: Oxacillin, PEN: Penicillin, RIF: Rifampicin, VAN: Vancomycin)

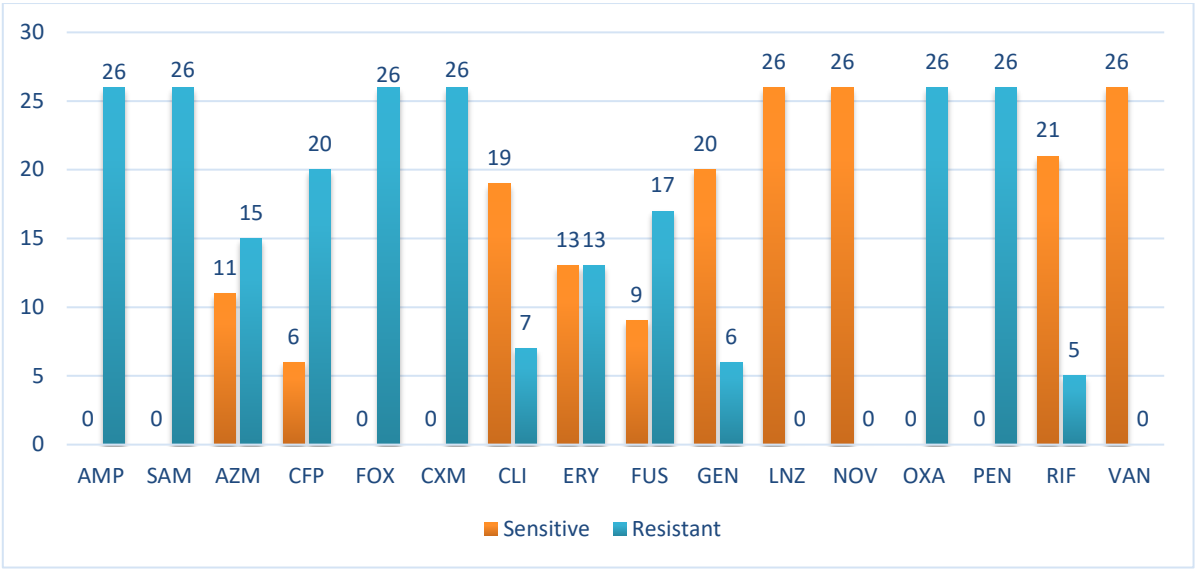

Fig. 2. Proportion of antibiotic susceptibility profiles among methicillin-resistant *S. aureus* (MRSA)
(AM: Ampicillin, SAM: Unasyn, AZM: Azithromycin, CFP: Cefoperazone, FOX: Cefoxitin, CXM: Cefuroxime, CLI: Clindamycin, ERY: Erythromycin, FUS: Fusidic acid, GEN: Gentamicin, LNZ: Linezolid, NOV: Novobiocin, OXA: Oxacillin, PEN: Penicillin, RIF: Rifampicin, VAN: Vancomycin)

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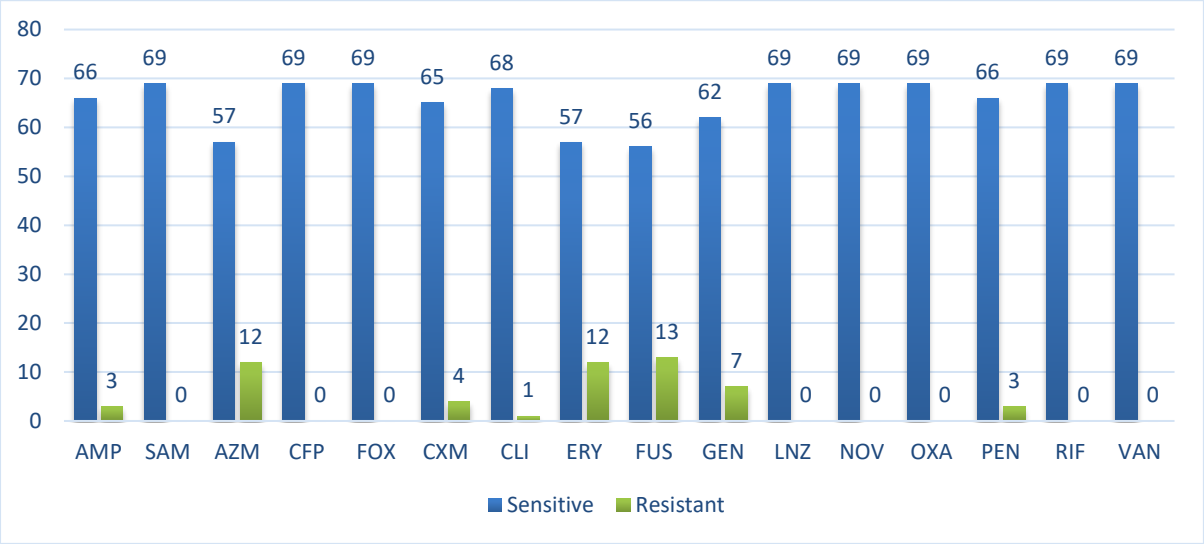

Fig. 3. Proportion of antibiotic susceptibility profiles among methicillin-sensitive *S. aureus* (MSSA)
(AM: Ampicillin, SAM: Unasyn, AZM: Azithromycin, CFP: Cefoperazone, FOX: Cefoxitin, CXM: Cefuroxime, CLI: Clindamycin, ERY: Erythromycin, FUS: Fusidic acid, GEN: Gentamicin, LNZ: Linezolid, NOV: Novobiocin, OXA: Oxacillin, PEN: Penicillin, RIF: Rifampicin, VAN: Vancomycin)

4.0 DISCUSSION

Staphylococcus aureus is recognized to be one of the most frequent pathogens that causes nosocomial infections globally including in Malaysian hospitals [7, 20]. An arising number of MRSA infections was encountered in Malaysian hospitals since the mid-1970s. The increment has been noted in large tertiary-care teaching hospitals as well as in community hospitals [20-21]. The ability of *S. aureus* to develop and acquire antimicrobial resistance has ushered to the emergence of multidrug resistant strains such as MRSA. The MRSA strains offer a challenge to physicians due to limited options of antibiotics for the treatment [3].

In this study, a total of 95 *S. aureus* strains were isolated from 3571 specimens for a period of 6 months. The overall rate of *S. aureus* recovery from the specimens was 2.66% and the prevalence of MRSA isolation was 27%. Our findings supported earlier studies data that reported the prevalence of MRSA in Malaysia ranged from 17% to 44.1% [7, 13]. Other earlier studies have reported a broad range of MRSA infection rates among hospitalized patients. In Asia-Pacific region, the rate was 45.9% and ranging from 5.0% in the Philippines to 79.5% in Hong Kong. Lower rates were reported in developed countries such as Latin America (34.9%), the United States (34.2%), Europe (26.3%) and Canada (5.7%) [13-14]. The differences might be due to few factors such as study sample size, populations, interpretation guidelines and bacterial culture techniques [22].

As reported in previous studies by Norazah et al., (2001) and Noordin et al., (2016), most of *S. aureus* from HATTM were isolated from pus and wound specimens (38.9%) [23-24]. Most of the patients with *S. aureus* infections were male patients (68.4%) and were from medical ward (40%). Majority of MRSA (49%) in this study was isolated from blood specimen. This finding is in concordance with results from previous studies where most of their MRSA isolates were obtained from blood culture [25-26]. Bacteraemia caused by MRSA is common in hospitals worldwide and is associated with high mortality rate as well as vancomycin treatment failure. In Malaysia, 21% cases of bacteraemia were reported to be caused by MRSA [25].

The present study discovered that age of patient as well as types of infection were associated significantly with the isolation of MRSA ($p < 0.05$). The two parameters are significant risk factors in the acquisition of MRSA. This agrees with results obtained from previous studies that suggested older patients will have higher risk of MRSA infections [23, 27]. In their study, MRSA infections were significantly increased in the age group of >50 years old. However, most MRSA strains in the study by Corea and Perera (2003) were HA-MRSA (59%) while in the present study, most of the MRSA were CA-MRSA (84.6%), with only 4 HA-MRSA isolates [27]. The low number of HA-MRSA isolation in the present study might be attributed to a strict compliance of nosocomial infection measures implemented in

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HATTM. These include isolation of all suspected or proven MRSA patients, education, hand hygiene, usage of effective disinfectant, surveillance activity and good quality of care [3, 23]. In addition, as reported by Rohani et al., (2000), a small hospital like HATTM mainly treat patients with community-acquired infections such as CA-MRSA infections [21}. In Malaysia, nosocomial infections by HA-MRSA were seen most commonly in tertiary-level care hospitals such as Hospital Kuala Lumpur and Hospital Tengku Ampuan Rahimah in Klang with higher number of patients [7, 22-23]. Majority of MRSA from present study were from medical ward (50%) in agreement with result from a recent study in [23]. In their study, most MRSA isolates were also from medical ward.

As reported elsewhere, the MRSA isolates from present study have higher resistance frequency to many antibiotics compared to MSSA isolates [4, 11, 13, 17]. Interestingly, all *S. aureus* isolates from this study including MRSA strains were sensitive to vancomycin and linezolid. In Malaysia, vancomycin and linezolid are the drug of choice to treat MRSA infections while cloxacillin is recommended for the treatment of MSSA infections, especially for adult patients in the ICU [7].

5.0 LIMITATIONS

There are some limitations in this study. This preliminary study involved *S. aureus* isolates obtained from specimens received by Department of Pathology, HATTM during a period of 6 months only. Future study with a larger sample size, within a wider study period need to be done to have a bigger picture of *S. aureus* antibiotic susceptibility profiles to confirm that vancomycin-resistant *S. aureus* is has not yet been established in HATTM.

6.0 CONCLUSIONS

Our results confirmed that vancomycin-resistant *S aureus* has not yet established in HATTM. The MRSA and MSSA susceptibility to antibiotics is different. We recommend the judicious use of antibiotics, restricting the use to only necessary cases. Correct selection of the antibiotics based on antibiotic susceptibility test results is crucial for effective treatment and prevention of resistance emergence in MRSA and MSSA. As for prophylactic measures, consistent follow-up and proper management of all patients suspected or proven to have MRSA infection should also be implemented. Future study with a larger sample size that include phenotypic and genotypic characterisation will provide an outright data for *S. aureus* infections monitoring.

7.0 CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

8.0 ACKNOWLEDGEMENT

This work was supported by the Short-Term Grant (UPNM/2019/GPJP/SP/1). The authors fully acknowledged Ministry of Higher Education (MOHE) and National Defence University of Malaysia (NDUM) for the approved fund which makes this research feasible. The authors also would like to thank the technical staff in every institution involved for their assistance.

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