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ORIGINAL ARTICLE

Prevalence of Methicillin-Resistant *Staphylococcus aureus* at a Tertiary Teaching Hospital in Malaysia

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ABSTRAK

Staphylococcus aureus rintang-Methicillin (MRSA) adalah patogen nosokomial utama yang menyebabkan morbiditi, kematian dan kadar kos perbelanjaan perubatan yang tinggi di kebanyakan hospital di seluruh dunia. Tujuan kajian ini adalah untuk menentukan kekerapan kadar jangkitan nosokomial MRSA, faktor-faktor yang berkaitan dan corak ketahanan antibiotik. Ini adalah analisis retrospektif pangkalan data organisma rintang pelbagai jenis ubat (MDRO) yang dikultur daripada pesakit-pesakit yang dimasukkan ke Hospital Canselor Tuanku Mukhriz (HCTM) selama 2 tahun (2018-2019). MRSA menyumbang kepada 23.6% daripada jumlah pemencilan MDRO. Lelaki mempunyai risiko yang lebih tinggi untuk dijangkiti oleh MRSA (p<0.05), manakala kadar paling prevalen MRSA adalah daripada wad ortopedik (47.5%) dan diikuti oleh wad perubatan (29.4%). Isolat MRSA yang diperolehi adalah diambil dari saluran pernafasan (55.6%) diikuti oleh tisu (50.8%) dan darah (27.8%). Semua isolat MRSA rintang terhadap antibiotik penicillin G, oxacillin diikuti oleh ciprofloxacin (83.8%) erythromycin (71.5%) dan clindamycin (53.5%). Isolat MRSA rentan terhadap antibiotik teicoplanin (99.7%), mupirocin (99.3%), co-trimoxazole (98.4%), rifampicin (97.8%), doxycycline (97.4%), linezolid (95.8%), gentamicin (93.9%) dan asid fusidik (86.2%). Trend kerentanan terhadap antibiotik bagi isolat MRSA di HCTM selama 2 tahun terakhir (2018 hingga 2019) tetap tidak berubah. Penyelidikan lebih lanjut diperlukan

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untuk menyiasat faktor-faktor penyebab kepada pembentukan MRSA dengan membezakan dengan jelas di antara jangkitan dan koloni MRSA, pembawaan MRSA di hospital dan di komuniti.

Kata kunci: antibiotik, jangkitan dalam hospital, kerentanan ubat antimikrob, Staphylococcus aureus rintang Methicillin

ABSTRACT

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major nosocomial pathogen that causes severe morbidity, mortality and high medical expenses in many hospitals worldwide. The present study aimed to determine the prevalence of MRSA nosocomial infection, its associated factors, and its antimicrobial susceptibility pattern. This was a retrospective analysis of a database of Multidrug-Resistant Organism (MDRO) that was cultured from patients admitted to Hospital Canselor Tuanku Mukhriz (HCTM) over a period of 2 years (2018-2019). MRSA accounted for 23.6% of total MDRO isolates. The male gender had a higher risk for MRSA acquisition ($p<0.05$), while the most prevalent setting for MRSA was the orthopaedic ward (47.5%) followed by the medical ward (29.4%). The MRSA strains were significantly isolated from respiratory specimens (55.6%) followed by tissue (50.8%) and blood (27.8%). All MRSA isolates were resistant to penicillin G, oxacillin followed by ciprofloxacin (83.8%) erythromycin (71.5%) and clindamycin (53.5%). MRSA isolates were most susceptible to teicoplanin (99.7%), mupirocin (99.3%), co-trimoxazole (98.4%), rifampicin (97.8%), doxycycline (97.4%), linezolid (95.8%), gentamicin (93.9%) and fusidic acid (86.2%). The trend for MRSA's antibiotic susceptibility in HCTM for the past 2 years (2018 to 2019) remains unchanged. Further research will be required to investigate the predictor of MRSA by clearly differentiating between MRSA infections and colonisations, hospital-acquired MRSA and community-acquired MRSA.

Keywords: antibiotics, antimicrobial drug resistance, hospital-acquired infection, methicillin resistant *Staphylococcus aureus*

INTRODUCTION

Staphylococcus aureus (*S. aureus*) is the major cause of gram-positive bacterial infections, generating a wide range of illnesses ranging from minor skin infections to life-threatening necrotising pneumonia. Historically, *S. aureus* infections were cured with common antibiotics but now the development of multidrug-resistant organisms is a serious matter. Multi Drug-resistant Organisms (MDRO) are predominantly bacterial pathogens that are resistant to one or more classes of antimicrobial agents with Methicillin-

Resistant *S. aureus* (MRSA) being one example. Although only endemic in a hospital setting initially, MRSA rapidly emerged in the communities in the 90s becoming a prevalent trend globally. (Siegel et al. 2006; Stefani et al. 2012; Liebowitz 2009; DeLeo & Chambers 2009).

The epidemiology of MRSA is apparently shifting as it is responsible for an increasing number of nosocomial infections especially in patients who are critically ill and Asia is among the highest-incidence regions in the world for MRSA (Diekema et al. 2001; Vincent et al. 1995; Chuang & Huang 2013; Bell et al. 2002). In Malaysia, MRSA has been reported to be the cause of 21% nosocomial bacteraemia cases (Ahmad et al. 2010). The overall rate of MRSA has increasing trend from 25.7% to 28.7%, 27.9% and 33.0% in 1996, 1998 and 2000, respectively, based on a cross-sectional study conducted in Hospital Kuala Lumpur (HKL), Hospital Tengku Ampuan Rahimah (HTAR), Klang and the Bacteriology Division at the Institute for Medical Research (IMR); all of which are located in the Klang Valley (Rohani et al. 2000). It has been shown that MRSA lengthens hospitalisation, leading to more adverse outcomes and higher costs (Cosgrove et al. 2005; Shorr et al. 2006). The MRSA isolates have showed resistance to a broad range of antibiotics, limited treatment options to very few agents such as vancomycin and teicoplanin (Brumfitt et al. 1989). Vancomycin has a constricted spectrum of activity that is limited to a majority of gram-positive bacteria and is a drug of choice for MRSA infection treatment.

Understanding the prevalence and antimicrobial susceptibility patterns of MRSA isolates is necessary for appropriate treatment decision and effective infection control as it has shown to affect the patient's outcome during hospitalisation and also the high medical expenses. In line with the above, the aim of this study was to determine the prevalence and associated factors MRSA strains isolated from clinical specimens in Hospital Canselor Tuanku Mukhriz (HCTM) as well as to evaluate its antimicrobial resistance profile. These findings can be a significant indicator on the control of nosocomial infections, provide pertinent input to complement the data on medical care-related infections, help flag abnormal warnings for appropriate interventions, and support public health in Malaysia.

MATERIALS AND METHODS

This study was carried out at HCTM, formerly known as Hospital Universiti Kebangsaan Malaysia, which is one of the four teaching university hospitals in Malaysia. It is located in Bandar Tun Razak, Kuala Lumpur with 1,040-bed capacity. This study was a retrospective review based on data reports of MDRO isolates that were collected from patients admitted to HCTM from January 2018 to December 2019. The isolation and identification od *S. aureus* were performed at HCTM's microbiology lab using standard bacteriologic culture methods. Definition of MRSA and other MDROs was based on the recently proposed joint definition by the European

Table 1: Distribution of types of MDROs isolates at HCTM, 2018 and 2019.

Organism (n=1556)	Frequency	Percentage (%)
ESBL	883	56.7
MRSA	367	23.6
Acinetobacter	122	7.8
Others MDR	78	5.0
MDR PAE	62	4.0
CRE	37	2.4
VRE	7	0.4

MRSA=Methicillin-resistant *S. aureus*; ESBL=Extended spectrum beta-lactamases; MDR PAE=Multidrug Resistance *Pseudomonas aeruginosa*; CRE=Carbapenem-resistant Enterobacteriaceae; VRE=Vancomycin-resistant enterococci

Centre for Disease Prevention and Control (ECDC) and the Centres for Disease Prevention and Control (CDC) (Magiorakos et al. 2012). In this study we analysed all strains of MDRO, which could come from infected and/or colonised patients.

Demographic data and factors associated with MRSA infection, such as age, sex, race, specimens, ward and department as well as antimicrobial susceptibility were collected from the Medical Microbiology and Parasitology Laboratory database. No duplicate isolates from the same patient and no environmental strains were included in this study. Exclusion criteria were patients below 18 years and outpatients from HCTM follow-up clinics. Disk diffusion method were applied to determined antimicrobial susceptibility testing of the isolates according to HCTM's Medical Microbiology and Parasitology Laboratory protocol. Antibiotics that were tested included gentamicin, ciprofloxacin, erythromycin, clindamycin, fusidic acid, penicillin G, rifampicin, oxacillin, doxycycline, mupirocin, linezolid, teicoplanin and co-trimoxazole.

Prevalence rates of MDRO isolates were calculated by dividing the number of cases with index by number of yearly inpatient admissions for the whole year. The prevalence rates

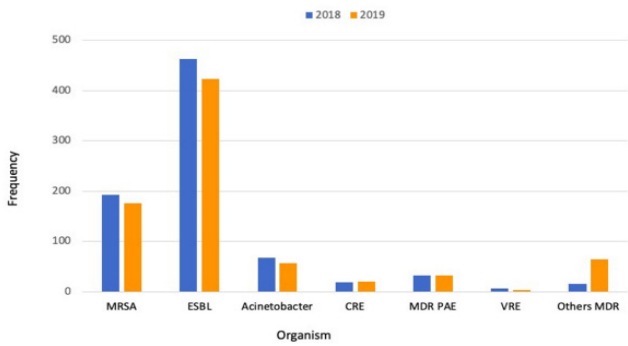

Figure 1: Isolated rates of MDROs in HCTM from 2018 to 2019 by organism.

Table 2: Prevalence of MRSA and non MRSA in term of socio-demography (gender, age, and race), specimen type, ward and department in HCTM

Variables	MRSA	Non-MRSA		
	Frequency (%)	Frequency (%)	χ^2	p
Gender				
Female	144 (21.0)	542 (79.0)	4.584	0.032*
Male	223 (25.6)	647 (74.4)		
Age (years)				
18-30	28 (24.3)	87 (75.7)	0.141	0.998
31-40	31 (22.5)	107 (77.5)		
41-50	36 (23.5)	117 (76.5)		
51-60	63 (23.6)	204 (76.4)		
>60	208 (23.7)	669 (76.3)		
Race				
Malay	193 (23.8)	619 (76.2)	1.400	0.705
Chinese	125 (22.8)	423 (77.2)		
Indian	40 (26.7)	110 (73.3)		
Others	9 (19.6)	37 (80.4)		
Specimens				
Blood	78 (27.8)	203 (72.2)	391.49	<0.05*
Urine	7 (2.1)	319 (97.9)		
Rectal	0 (0.0)	343 (100)		
Tissue	66 (50.8)	64 (49.2)		
Respiratory	115 (55.6)	92 (44.4)		
Others	101 (37.5)	168 (62.5)		
Ward				
General Ward	277 (29.8)	651 (70.2)	57.91	<0.05*
Intensive Care	64 (12.2)	460 (87.8)		
Others	26 (25.0)	78 (75.0)		
Department				
Intensive Care	59 (11.5)	456 (88.5)	114.81	<0.05*
Medical	102 (29.4)	245 (70.6)		
Surgical	59 (20.0)	236 (80.0)		
Orthopaedic	95 (47.5)	105 (52.5)		
Others	52 (26.1)	147 (73.9)		

*significant p<0.05 (Pearson Chi Square)

were reported per 1,000 admissions. Chi Square test was used to compare prevalence of MRSA and non-MRSA strains between patient's demography, specimen, hospital ward type and department which can be used as the associating factor. SPSS version 23 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses with $p<0.05$ considered statistically significant.

RESULTS

From January 2018 to December 2019, MRSA was the second highest strain discovered among patients admitted to HCTM following extended spectrum beta-lactamases (ESBL) (Table 1). In the same period, the trend of MRSA isolates has decreased, so have ESBL, Acinetobacter and Vancomycin-resistant enterococci (VRE). Carbapenem-resistant

Table 3: Sensitivity Pattern of MRSA isolate at HCTM (2018-2019)

Antibiotics	Total Isolated Case	Sensitive (%)	Resistant (%)
Teicoplanin	307	306 (99.7)	0 (0)
Mupirocin	324	322 (99.3)	2 (0.6)
Co-Trimoxazole	317	312 (98.4)	2 (0.6)
Rifampicin	312	305 (97.8)	7 (2.2)
Doxycycline	312	304 (97.4)	4 (1.28)
Linezolid	300	299 (95.8)	1 (0.3)
Gentamicin	312	293 (93.9)	17 (5.4)
Fusidic Acid	312	269 (86.2)	43 (13.8)
Clindamycin	312	139 (44.5)	167 (53.5)
Erythromycin	312	88 (28.2)	223 (71.5)
Ciprofloxacin	303	47 (15.5)	254 (83.8)
Oxacillin	333	0 (0)	333 (100)
Penicillin G	312	0 (0)	312 (100)

Enterobacteriaceae (CRE) and multidrug resistance *Pseudomonas aeruginosa* (MDR PAE) remained stagnant, while other types of MDR increased (Figure 1).

A total of 1556 non duplicate MDRO isolates (infected/colonised), which included 367 (23.6%) MRSA and 1,189 (76.4%) non MRSA (ESBL, VRE, CRE, MDR PAE, Acinetobacter and other types of multi drug resistant organism) were isolated from different clinical specimens that were sent to the Microbiology Laboratory. The prevalence of MRSA was significantly higher in respiratory specimens and patients residing in general wards, specifically in the Orthopaedic department (Table 2). Male patients were noted to have an increased risk of contracting MRSA compared to females (Table 2). The age groups of patients and race were found not to be significantly associated.

Table 3 represents the distribution of MRSA isolates antibiotic susceptibility.

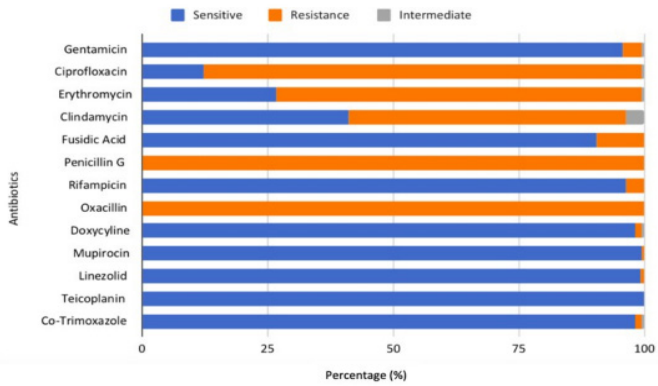

Figure 2: MRSA's antibiotic susceptibility in 2018

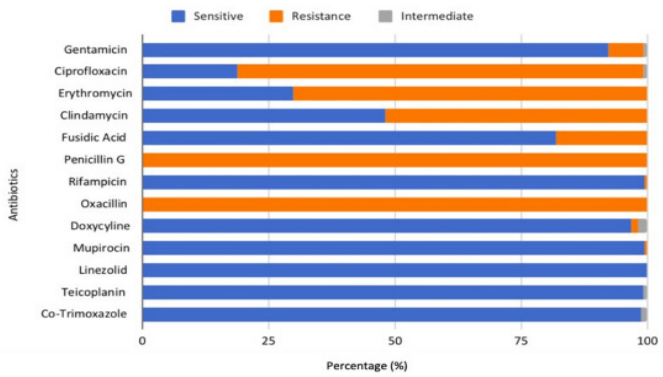

Figure 3: MRSA's antibiotic susceptibility in 2019

All MRSA isolates were resistant to penicillin G and oxacillin (100%), followed by ciprofloxacin (83.8%) erythromycin (71.5%) and clindamycin (53.5%). In this study, it was found that MRSA isolates were susceptible to teicoplanin (99.7%), mupirocin (99.3%), co-trimoxazole (98.4%), rifampicin (97.8%), doxycycline (97.4%), linezolid (95.8%), gentamicin (93.9%) and fusidic acid (86.2%). The trend for MRSA's antibiotic susceptibility in HCTM for the past 2 years (2018 to 2019) remained unchanged (Figures 2 & 3).

DISCUSSION

The World Health Organisation (WHO) now affirms that MDROs throughout every geographic region of the world are a rising threat (Chan 2017). Drug-resistant bacterias pose a serious risk to public health globally because of their potential to colonise humans without causing symptoms, their environmental endurance and the clinical threat that they may give rise to. Among them, MRSA is responsible for a large proportion of nosocomial infections, which are complicated and expensive to treat (Cosgrove et al. 2005; Gall et al. 2020; Al-Talib et al. 2009). Since its emergence in 1961, there has been a steady increase of MRSA worldwide, including Malaysia, with increasing reports from large tertiary-care teaching hospitals to small community hospitals (Stefani et al. 2012; Cheong et al. 1994). However, out of 1556 non-duplicate MDRO isolates in the present study, 367 (23.6%) were MRSA strains with a decreasing trend observed over the 2 year study period. This could be credited to HCTM nosocomial infection committee's updated prophylactic efforts, improved awareness and practice of preventive measures such as hand hygiene for staff as wll as the quality of care in general.

Among MRSA isolates at HCTM, male patients were found to have increased risk of contracting MRSA compared to females, which is in coherence with a 2017 study at another Malaysian tertiary teaching hospital (Sit et al. 2017). Existing literature has shown that the large proportions of risk factors, which predispose individuals

to acquire MRSA, were predominantly found in males rather than females. For example, diabetes mellitus related terminal renal failure, requiring dialysis which added to the risk profile, was more common in men (Van Landeghem et al. 2005). Furthermore, Hornberg et al. (2003) demonstrated that peripheral vascular disease in diabetics was four times more common in men, resulting in delayed healing of the wound with prolonged or repeated days of hospitalisation. These two factors add to the risk profile for MRSA (Fascia et al. 2009; Hornberg et al. 2003). However our findings were in contrast with previous MRSA studies in Brazil, Israel and Singapore that showed no significant gender predominance (Cavalcanti et al. 2005; Aizen et al. 2007; Lye et al. 1993). These variations might be attributed to different sample populations.

The prevalence of MRSA isolates in patients who were admitted to the general ward, specifically in the Orthopaedic Department, was significantly higher followed by the general ward at the Medical Department. This finding was similar to a study of MRSA nosocomial infection trends at Hospital Universiti Sains Malaysia (HUSM) from 2002 to 2007 (Al-Talib et al. 2010). Since medical staff are almost always the carriers of MRSA, the high prevalence in the wards of the Orthopaedic and Medical Departments could be related to the struggles of maintaining appropriate standard of hygiene and cross-infection among staff members who may have been asymptomatic carriers of MRSA (Albrich & Harbarth 2008). In other earlier literature, intensive care units (ICU) had the highest infection rates of MRSA (Kupfer et al. 2010; Dibah et al. 2014). The high risk of MRSA in the ICU was very likely due to the preselected patient cohort with a higher number of risk factors and comorbidities (Thompson et al. 2008; Bloemendaal et al. 2009). Other factors include prolonged hospitalisation, use of invasive devices, high multi-resistant bacteria prevalence and increased antibiotic use (Sadoyama et al. 2008; Nicastri et al. 2008).

In the present study, 115 (55.6%) MRSA isolates were found from respiratory specimens (nasal swab, sputum and tracheal aspirate) followed by tissue and blood. This is congruent with the fact that *S. aureus* most frequently causes skin or soft tissue, respiratory tract and bloodstream infections (Tong et al. 2015). The sources of MRSA isolates have shown variations across a number of studies with differences in study design and population attributed (Dilnessa & Bitew 2016). Notable limitation to Dilnessa & Bitew (2016) finding is that the type of infection associated with the collection of test samples (e.g. blood samples collected from patients with respiratory infections are not distinguished from those collected from patients with bacteraemia) were not considered and analysed because of lack of data.

Isolates of *S. aureus* were tested against 13 different antibiotics at HCTM. As expected, MRSA isolates were completely resistant to penicillin G and oxacillin. This was followed by ciprofloxacin (83.8%), erythromycin

(71.5%) and clindamycin (53.5%). This was a stark contrast to a 1996 study conducted on the susceptibility and resistance of antibiotics against MRSA in the Klang Valley, where susceptibility to penicillin was about 3 to 10% and the percentage of resistance to ciprofloxacin (29.2%), erythromycin (45.9%) and clindamycin (2.1%) were much lower (Rohani et al. 2000). It is reassuring that many of the isolates in the present study remained sensitive to a number of standard anti-MRSA antibiotics available at HCTM which include teicoplanin, mupirocin, co-trimoxazole, rifampicin, doxycycline, linezolid, gentamicin and fusidic acid. Unlike a similar study in HUSM, where co-trimoxazole had already become practically ineffective (Al-Talib et al. 2010). In addition, the pattern of MRSA antibiotic susceptibility at HCTM throughout the past two years (2018-2019) remained consistent, reflecting sensible use of antibiotics here.

One limitation of the present study was it only involved data from one tertiary teaching hospital which is also a referral hospital, thus not reflect the true MRSA prevalence and associated factors of the population. Additionally, the data used was not able to distinguish between active infection and colonisation. We also did not correlate the samples with detailed admission data for each patient which could have provided a more accurate description of community versus nosocomial infection onset. Hence, a prospective, case-controlled, multicentre study would be useful to confirm our findings.

CONCLUSION

Methicillin-resistant Staphylococcus aureus is a challenge from both clinical and epidemiological standpoints. In contrast to most literature, MRSA prevalence at HCTM is in a declining trend whereby the prevalence were 23.6% which could be due to the improved awareness and preventive protocol. The sensible use of antibiotics could also contribute to the consistent trend of MRSA's antibiotic susceptibility at HCTM from 2018 and 2019. We have been able to establish that male gender was significantly associated with heightened risk of MRSA acquisition, the most prevalent setting for MRSA being the general ward of the Orthopaedic Department and that MRSA strains were significantly isolated from respiratory specimens. Further research will be required to investigate the predictors of MRSA by clearly differentiating between MRSA infections and colonisations, hospital-acquired MRSA and community-acquired MRSA.

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