PREVALENCE AND ANTIBIOGRAM PROFILES OF *STAPHYLOCOCCUS AUREUS* ISOLATES FROM PATIENTS AT TAKSIN HOSPITAL, BANGKOK, THAILAND (JANUARY 2019 - MAY 2020)

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Abstract. *Staphylococcus aureus* is one of the most important bacteria that cause disease in humans. A total of 700 clinical *S. aureus* positive sputum (52.0%), pus (28.5%) and blood (14.8%) samples collected from patients who visited and/or were admitted to a tertiary care hospital, Bangkok, Thailand during January 2019 - May 2020 for the treatment of their illnesses were studied for their antibiogram profile. It was found that they were mostly methicillin-susceptible (MSSA) (77.1%) and those resistant to methicillin (MRSA) demonstrated sensitivity (70-100%) to fosfomycin, fusidic acid, gentamycin, tetracycline, trimethoprim-sulfamethoxazole, and vancomycin [minimum inhibitory concentration (MIC) range, MIC_{50} and MIC_{90} = 0.25-2.0, 0.5 and 1.0 μg/ml using E-test] and resistance to ciprofloxacin, clindamycin, and erythromycin. MSSA isolates were sensitive (88-100%) to all test drugs except tetracycline. MSSA (7%) and MRSA (90%) isolates exhibited multiple drug resistance (MDR) phenotype, among the former group the most common MDR pattern was against clindamycin + erythromycin + tetracycline (4%), followed by clindamycin + erythromycin + fosfomycin (1%) and clindamycin + erythromycin + gentamycin + tetracycline (1%) while among the latter the most common MDR pattern was against ciprofloxacin + clindamycin + erythromycin (55%), followed by ciprofloxacin + clindamycin + erythromycin + fosfomycin (18%). Inducible lincosamides, macrolides and streptogramin B resistance (iMLSB) phenotypes were present in 3 and 10% of MSSA and MRSA isolates respectively, while constitutive MLSB (cMLSB) resistance phenotype in 8 and 79% respectively. In conclusion, the findings demonstrate a high percent MRSA isolates concomitant with MDR phenotypes among clinical *S. aureus* from various samples at a hospital in Bangkok.

Keywords: *Staphylococcus aureus*, antibiogram profile, drug resistance, methicillin resistance, clinical isolate, Thailand

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INTRODUCTION

Staphylococcus aureus is a virulent Gram-positive bacterial pathogen, which is the leading cause of bloodstream infections and other severe infections in various tissues, *eg* joint fluid, lung, skin, and surgical sites (Durmaz *et al*, 2014). *S. aureus* can be divided into two types, methicillin-susceptible (MSSA) and methicillin-resistant (MRSA), the latter also possessing resistance to other antimicrobial agents [multidrug (MDR) resistance] (Becker *et al*, 2015). MRSA resistance to all beta-lactam antimicrobials is due to carriage of *mec*A, encoding a penicillin-binding protein (PBP2a) with low binding affinity for anti-beta-lactams, although in rare cases resistance to methicillin results from expression of *mec*C (CLSI, 2019; Cong *et al*, 2020). The first MRSA strain was reported in 1961 from a staphylococcal clinical isolate in the United Kingdom (Jevons, 1961), and since then MRSA has spread worldwide, being present in Africa, Asia, Europe, the Middle East, and USA (Lakhundi and Zhang, 2018; Guo *et al*, 2020).

Lincosamides, macrolides and streptogramin B are often used to treat staphylococcal diseases (Yilmaz *et al*, 2007; Mallikarjun *et al*, 2015). Resistance to macrolides in *S. aureus* occurs by two mechanisms, namely, post-transcriptional methylation of 23S bacterial ribosomal RNA leading to cross-resistance to macrolides, lincosamides and streptogramin B (MLSB-resistant phenotype) and an efflux mechanism (Weisblum, 1995). An MLSB resistance mechanism can be constitutive or inducible (*eg* by erythromycin) (Shidiki *et al*, 2019). Treatment failure can occur if inducible MLSB resistance mechanism is not identified (usually by specific microbiological techniques) (Vandana *et al*, 2009). Standard antibiogram profiling may not detect inducible MLSB phenotype.

Nosocomial MRSA has serious health and economic impacts (Al Bshabshe *et al*, 2020). A 1998 - 2001 survey of 32 hospitals in Thailand observed MRSA prevalence of 24-36%, and a January - May 2005 survey at Siriraj Hospital, Bangkok, central Thailand, revealed a higher prevalence, 41.5% (Mekviwattanawong *et al*, 2006). A subsequent study (August 2012 - July 2015) at Thammasat University Hospital, Pathum Thani Province (adjacent to Bangkok) found even higher MRSA prevalence, 46% (Phokhaphan *et al*, 2017). However, there was a declining trend, a MRSA prevalence of 38% was observed at Thammasat University Hospital in 2015 in the same study, and a 2017 survey at Chulalongkorn Memorial Hospital (a tertiary care university hospital in Bangkok) reported MRSA prevalence of 17% (Waitayangkoon *et al*, 2020). Outside Bangkok, a 2006 - 2014 survey in two provinces, namely, Sa Kaeo Province (in eastern Thailand,

near Cambodian border) and Nakhon Phanom Province (in northeastern Thailand, near Lao PDR border) reported prevalence of 10% for MRSA in clinical samples (Jaganath *et al*, 2018).

Here, prevalence and antibiogram profiles of *S. aureus* isolates from patients at a national tertiary-referral hospital in Bangkok during January 2019 - May 2020 were investigated. The findings should be a step towards evidence-based treatment of *S. aureus* infection, thereby avoiding empirical therapy and inducement of drug resistance.

MATERIALS AND METHODS

Samples collection

Clinical specimens of patients who were admitted in wards or treated at Outpatient Department in Taksin Hospital for their illnesses between 1 January 2019 and 31 May 2020 were collected. *S. aureus* was isolated and identified according to standard microbiological techniques (Becker *et al*, 2015). *S. aureus* isolates from different clinical samples of the same patient were counted as a single sample. Sputum was accepted for culture if containing >25 polymorphonuclear cells and <25 epithelial cells per light microscope field (100x magnification). For quantitative culture of urine, a 1 µl aliquot of calibrated loop was used. Confirmatory catalase and slide coagulase tests were used; if result of the slide coagulase test was negative, a tube coagulase test was performed (Becker *et al*, 2015).

The study protocol was approved by the Human Research Ethics Committee, Faculty of Pharmacy, Siam University (approval no. SIAMPY-IRB 2020/007) and that of the Bangkok Metropolitan Administration (approval no. E009h/63_NA). Informed consent was waived since the investigators used the specimens archived at the Microbiological Laboratory of Taksin Hospital and permission to use those specimens was granted by Director of Taksin Hospital.

Antibiogram profiling and D-test assay

Disk diffusion susceptibility test was performed according to Clinical and Laboratory Standards Institute guidelines (CLSI, 2019) using disks (Oxoid, Hampshire, United Kingdom and Becton Dickinson, Franklin Lakes, NJ) each containing ciprofloxacin (5 µg), clindamycin (2 µg), erythromycin (15 µg), fosfomycin (50 µg), fusidic acid (10 µg), gentamycin (10 µg), tetracycline (30 µg), and trimethoprim/sulfamethoxazole (1.25/23.75 µg). Minimum inhibitory concentration (MIC) of vancomycin was determined using MIC strip test (E-test, BioMerieux, Durham, NC). MRSA is defined if resistant to cefoxitin disk (30 µg) (CLSI, 2019) and an isolate multidrug-resistant (MDR) if resistant ≥3 classes of drugs (Seng *et al*, 2018).

Identification of *S. aureus mec*A

DNA was extracted from a loopful of colonies of each isolate grown on a 16-18-hour culture of sheep blood agar (Oxoid, Hampshire, United Kingdom). PCR amplification was carried using *S. aureus mec*A specific primers as previously described (Ishino *et al*, 2002) and 863-bp amplicon was analyzed by 1% agarose gel-electrophoresis and ethidium bromide staining.

D-test assay

A D-test was employed to detect inducible MLSB resistance using erythromycin (15 μg) and clindamycin (15 μg) disks (Oxoid, Hampshire, United Kingdom) on a 0.5 McFarland standard bacterial suspension cultured on Mueller Hinton agar (Oxoid, Hampshire, United Kingdom) (Motamedifar *et al*, 2014; CLSI, 2019; Shidiki *et al*, 2019).

RESULTS

Patients (n = 700) were 16 days to 100 years of age, with MSSA and MRSA prevalence of 77.1 (540 isolates) and 22.9% (160 isolates) respectively. MRSA isolates came mainly (86.9%) from patients >50 years of age (Fig 1). All randomly picked MRSA isolates (n = 40) were positive for carriage of *mec*A (data not shown). The three most common clinical specimens were sputum (52%), pus (28.5%), and blood (14.8%) (Fig 2). Range of urine *S. aureus* quantitative culture was from $<10^3$ to $\geq 10^5$ CFU/ml.

MSSA isolates were sensitive to all eight drugs tested except tetracycline whereas MRSA were sensitive to five and resistant to three test drugs (Table 1). MRSA vancomycin MIC range, MIC_{50} and MIC_{90} value was 0.25–2.0, 0.5 and 1.0 μg/ml, respectively and interpreted as sensitive (CLSI, 2019). MRSA isolates demonstrated higher percent MDR phenotypes compared to MSSA, with the former having 16 MDR patterns, most common being (ciprofloxacin + clindamycin + erythromycin) followed by (ciprofloxacin + clindamycin + erythromycin + fosfomycin), accounting for 105/144 (73%) MDR isolates, while the latter having 11 MDR patterns, the most common being (clindamycin + erythromycin +

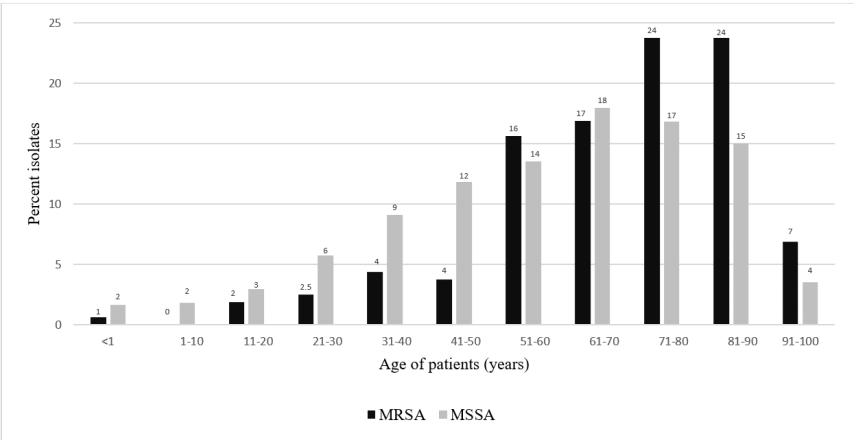

Fig 1 - Prevalence of methicillin-resistant *Staphylococcus aureus* (MSSA) and methicillin-sensitive *S. aureus* (MSSA) from clinical samples (n = 700), Taksin Hospital, Bangkok, Thailand (1 January 2019 - 31 May 2020)

MRSA is defined if resistant to cefoxitin disk (30 μg) (CLSI, 2019).

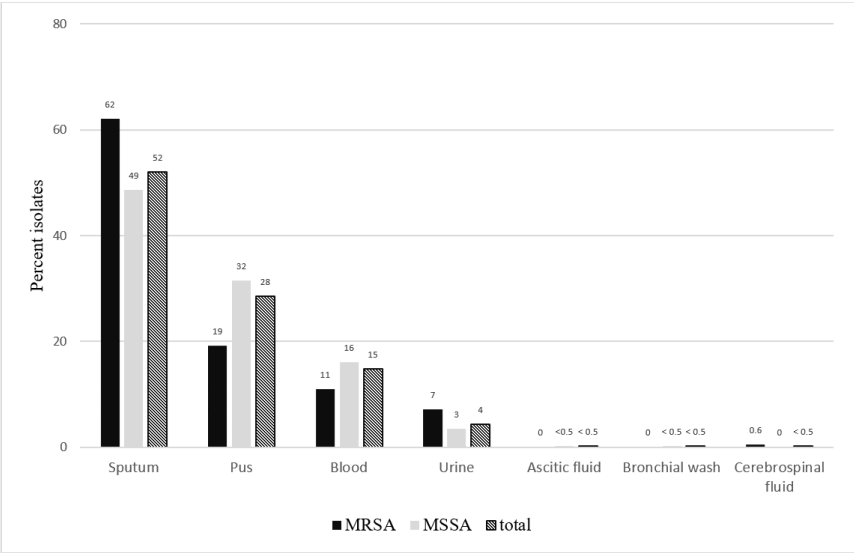

Fig 2 - Clinical sources of methicillin-resistant *Staphylococcus aureus* (MSSA) and methicillin-sensitive *S. aureus* (MSSA) (n = 700), Taksin Hospital, Bangkok, Thailand (1 January 2019 - 31 May 2020)

MRSA is defined if resistant to cefoxitin disk (30 μg) (CLSI, 2019).

tetracycline) followed by (clindamycin + erythromycin + fosfomycin) and (clindamycin + erythromycin + gentamycin + tetracycline), accounting for 28/41 (68%) MDR isolates (Table 1).

Inducible MLSB phenotype was present in 15 (3%) and 16 (10%) of MSSA and MRSA isolates respectively, and constitutive phenotype in 43 (8%) and 128 (79%) respectively (Table 2). Macrolide and streptogramin resistance or MS phenotype were present in 5 (1%) and 14 (8%) MSSA and MRSA isolates respectively.

DISCUSSION

In general, patients with MRSA infections have longer hospital stays, increasing health care costs. In USA, the Centers for Disease Control and Prevention considers MRSA an antibiotic resistance threat, accounting in 2019 for 323,700 hospitalized cases and 10,600 deaths (CDC, 2019). The Canadian Antimicrobial Resistance Surveillance System reported MRSA isolates from blood specimens increase from 0.40 cases/10,000 patients in 2014 to 0.51 cases/10,000 patients in 2018, with 24.3% patients with MRSA infection dying within one month of hospital admission (Public Health Agency of Canada, 2020).

In the present study, MRSA isolates accounted for 22.9% of all test *S. aureus* isolates, similar to that reported in Brazil (20.7%) (Bottega *et al*, 2014), Indonesia

Table 1

Antibiogram profiles of clinical *Staphylococcus aureus* isolates from Taksin Hospital, Bangkok, Thailand (1 January 2019 - 31 May 2020)

Drug#	MRSA Number resistant (%) (n = 160)	MSSA Number resistant (%) (n = 540)
CIP	152 (95)	56 (10)
CL	142 (89)	58 (11)
ER	144 (90)	63 (12)
FOS	48 (30)	8 (1.5)
FUS	0 (0)	2 (<0.5)
GEN	29 (18)	10 (2)
STX	6 (4)	0 (0)
TET	28 (17.5)	186 (34)
CIP + CL + ER	79 (49)	2 (<0.5)
CIP* + CL + ER	0 (0)	1 (<0.5)
CIP + CL + ER*	0 (0)	1 (<0.5)
CIP* + SXT + TET	0 (0)	1 (<0.5)
CIP + CL + ER + FOS	26 (16)	1 (<0.5)
CIP +CL+ ER + FOS*	4 (2.5)	0 (0)
CIP* + CL + ER + TET	0 (0)	1 (<0.5)
CIP + CL + ER + FOS + GEN	3 (2)	2 (<0.5)
CIP + CL + ER +FOS + TET	0 (0)	2 (<0.5)
CIP + CL + ER + FOS* + GEN + SXT* + TET	1 (0.5)	0 (0)
CIP + CL + ER + FOS + GEN + TET	8 (5)	0 (0)
CIP + CL + ER + FOS + GEN + TET*	2 (1)	0 (0)
CIP + CL + ER + GEN	5 (3)	0 (0)
CIP + CL + ER + GEN*	1 (0.5)	0 (0)
CIP + CL + ER + TET	3 (2)	0 (0)
CIP + CL + ER +GEN + SXT+ TET	2 (1)	0 (0)
CIP + CL + ER +GEN + SXT* + TET	1 (0.5)	0 (0)
CIP + CL + ER +GEN + TET	2 (1)	0 (0)
CIP +CL + GEN + TET	1 (0.5)	0 (0)
CIP + CL + TET	1 (0.5)	0 (0)
CL + ER + FOS	0 (0)	4 (1)

Table 1 (cont)

Drug#	MRSA Number resistant (%) (n = 160)	MSSA Number resistant (%) (n = 540)
CL + ER + TET	5 (3)	20 (4)
CL* +ER + TET	0 (0)	1 (<0.5)
CL + ER + GEN + TET	0 (0)	4 (1)
GEN* + SXT + TET	0 (0)	1 (<0.5)

#Multidrug resistance: ≥3 classes of drugs; *Intermediate resistance
CIP: ciprofloxacin; CL: clindamycin; ER: erythromycin; FOS: fosfomycin; FUS: fusidic acid; GEN: gentamycin; MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-sensitive *Staphylococcus aureus*; SXT: trimethoprim/sulfamethoxazole; TET: tetracycline

Table 2

Macrolides, lincosamides and streptogramin B (MLSB) resistance phenotypes of clinical *Staphylococcus aureus* isolates from Taksin Hospital, Bangkok, Thailand (1 January 2019 - 31 May 2020)

Phenotype	MRSA Number (%) (n = 160)	MSSA Number (%) (n = 540)	Total Number (%) (n = 700)
CL-S, ER-R D+ (inducible MLSB)	16 (10)	15 (3)	31 (5)
CL-R, ER-R (constitutive MLSB)	126 (79)	43 (8)	169 (24)
CL-S, ER-R (D-test)	4 (2)	5 (1)	9 (1)
CL-S, ER-S	14 (9)	477 (88)	491 (70)
Total	160 (100)	540 (100)	700 (100)

CL: clindamycin; D: disk diffusion induction test; ER: erythromycin; MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-sensitive *Staphylococcus aureus*; R: resistant; S: sensitive

(28%) (Suryatenggara *et al*, 2018) and Turkey (20.9%) (Durmaz *et al*, 2014), but lower than in Ethiopia (68.4%) (Tadesse *et al*, 2018), India (38.24%) (Mallikarjun *et al*, 2015), Iraq (42.5%) (Pirko *et al*, 2019), Nepal (78.06%) (Shidiki *et al*, 2019), and Nigeria (56.4%) (Chika *et al*, 2018). In Thailand, a recent study at Thammasat University Hospital, Pathum Thani province (adjacent to Bangkok) reported a prevalence of 46% (Phokhaphan *et al*, 2017). The difference between their study and our study may be due to drug usage policy or type of hospitals. Age and gender of patients susceptible to MRSA infection are unpredictable and vary according to geographical locations (Pomorska-Wesołowska *et al*, 2017; Gu *et al*, 2020), but are more common in adults.

The present study observed the majority of MRSA isolates was from sputum, similar to other reports (23-71%) from Thailand (Mekviwattanawong *et al*, 2006; Phokhaphan *et al*, 2017; Waitayangkoon *et al*, 2020), but pus was the predominant source from out-patients in a report from Nepal (Regmi *et al*, 2020). Again, different health status and geographical features between the two countries could account for the observations.

Percent MRSA isolates exhibiting resistance to ciprofloxacin and clindamycin was higher than that (79 and 66% respectively) reported in China, but percent MSSA isolates sensitive to the test battery of antimicrobials was similar to other reports in the country (Mekviwattanawong *et al*, 2006) and in Shanghai, China (Gu *et al*, 2020). Data for MDR patterns in MRSA and MSSA are scarce in Thailand, but a recent study conducted in hospitals of Masovian district in Poland observed 92.9% of MRSA isolates showed MDR phenotypes, the predominant drug resistance pattern was (ciprofloxacin + clindamycin + erythromycin + levofloxacin) (Kot *et al*, 2020).

The prevalence of iMLSB in MSSA and MRSA noted in the present study was comparable with that (2.9 and 11.8% respectively) reported in India (Mallikarjun *et al*, 2015). In Iran, iMLSB *S. aureus* increased from 7.5% in 2013 to 21.7% in 2018 (Goudarzi *et al*, 2020), and in Nepal both iMLSB and cMLSB were more prevalent among MRSA than MSSA (43.80% and 26.85%, and 40.62% and 10.93%respectively) (Shidiki *et al*, 2019).

In conclusion, the survey shows prevalence of MRSA in a hospital setting in Bangkok was high (nearly a quarter of all *S. aureus* isolates examined) and determination of current antibiogram profiles are needed to avoid ineffective empirical antibiotic drug treatment, given the virulent nature of MRSA infection.

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CONFLICTS OF INTERST DISCLOSURRE

The authors declare no conflicts of interest.

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