PREVALENCE OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* AND OTHER STAPHYLOCOCCAL NASAL CARRIAGES AMONG HEALTH-CARE WORKERS, PHRAMONGKUTKLAO HOSPITAL

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Abstract

Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) is a group of *S. aureus* strains containing the SCC*mec* gene causing beta-lactam antibiotic resistance. MRSA is common in healthcare settings and can cause serious problems.

Objective: The study aimed to investigate the prevalence of MRSA nasal colonization among privates of the Medical Private Company, Phramongkutklao Hospital, including antibiotic susceptibility pattern of *S. aureus* isolates and risk factors of *S. aureus* nasal carriage.

Methods: Nasal swabs were obtained from the anterior nares of 170 privates. Staphylococcal isolates were identified using a catalase test, tube coagulase test and matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS). MRSA detection was screened using cefoxitin disk diffusion and confirmed using the *mec*A gene detection and SCC*mec* typing. Antibiotic susceptibility patterns of *S. aureus* were examined using the disk diffusion method. A questionnaire was collected from the subjects to determine risk factors for *S. aureus* nasal carriage.

Results: Of 170 subjects, 157 (92.35%) revealed staphylococcal positive, yielding 161 staphylococcal isolates. The prevalence of MRSA, methicillin-resistant *Staphylococcus epidermidis* (MRSE), and methicillin-susceptible *Staphylococcus aureus* (MSSA) nasal carriage was 0.59, 1.18 and 8.82%, respectively. The MRSA isolate carried *mecA* revealing SCC*mec* type II. The MSSA isolates indicated low resistance to tetracycline (13.3%), whereas the MRSA isolate resisted ciprofloxacin, clindamycin, erythromycin, gentamicin, oxacillin and tetracycline. Using multiple logistic regression analysis, a significant risk factor for *S. aureus* nasal carriage was utensil sharing (adjusted odds ratio=4.41; 95% CI=1.33-14.61).

Conclusion: Healthcare-associated MRSA existed among privates of the Medical Private Company. An associated risk factor for acquiring *S. aureus* was utensil sharing which could be used to help improve prevention and control management among privates.

Keywords: MRSA, MALDI-TOF MS, *Staphylococcus epidermidis*, MSSA, *mecA* gene, SCC*mec*

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Introduction

Staphylococci are gram-positive bacteria in the genus *Staphylococcus,* under the bacterial family Staphylococcaceae.[1] Fifty-nine species of staphylococci are widespread in nature.[2] Their significant natural habitats are mammals' skin and mucous membranes, including humans.[3] Staphylococcal species generally associated with human infections are *S. aureus*, *S. epidermidis* and *S. saprophyticus*.[4] Others may also be related to human diseases such as *S. haemolyticus*, *S. hominis*, *S. simulans* and *S. warneri*.[5] *S. aureus,* one of the most important bacterial pathogens among humans, causes various diseases ranging from mild skin and soft tissue infections (SSTIs) to severe life-threatening diseases such as complicated SSTIs, osteomyelitis, bacteremia, infective endocarditis and toxic shock syndrome.[6] Among humans, it commonly inhabits the nasal cavity and skin surface.[7] Most strains of *S. aureus* have developed antibiotic resistance, creating a serious problem for treatments, especially those that resist methicillin (methicillin-resistant *Staphylococcus aureus* or MRSA).[8]

Since the first MRSA report in 1961, MRSA has been one of the essential causative pathogens of healthcare-associated infections (HAIs) affecting patients and healthcare systems worldwide.[9, 10] MRSA infections are capable of causing severe infections such as osteomyelitis, endocarditis, pneumonia and sepsis, all of which could ultimately lead to mortality.[11] MRSA is multidrug-resistant (MDR), not only resists beta-lactams such as penicillin and cephalosporins but also resists nonbeta-lactam antibiotics such as macrolides, lincosamides, quinolones, tetracyclines and aminoglycosides.[12] According to a recent study, MRSA was susceptible to vancomycin (100%), mupirocin and rifampicin (99.2%), followed by chloramphenicol (82.3%) and gentamicin (76%).[13] Thus, vancomycin injection is the first drug of choice for MRSA infections; mupirocin nebulization is a widely used treatment for MRSA nasal colonization.

The methicillin-resistance mechanism is the production of an altered penicillin-binding protein (PBP) from PBP-2 turning into PBP-2a, and decreasing affinity to betalactams. The *mec*A gene encodes this protein on a mobile genetic element named Staphylococcal Cassette Chromosome *mec* (SCC*mec*).[14] To date, 13 different SCC*mec* types (I-XIII) have been identified.[15] In Thailand, most SCC*mec* were IIIA and IIA types.[16] On the other hand, other staphylococci can also carry this SCC*mec* and have the property of being methicillin-resistance such as methicillin-resistant *S. epidermidis* (MRSE), which is a kind of methicillin-resistant coagulase-negative staphylococci (MRCoNS). For this reason, MSSA can become MRSA upon obtaining the SCC*mec* from MRSA or MRCoNS.[17]

Hospital-acquired MRSA (HA-MRSA) is generally defined as those that develop infections within 48 hours of discharge from a hospital, clinic or healthcare facility. Community-acquired MRSA (CA-MRSA) among healthy individuals stems from those who have not been hospitalized or had a medical procedure within the past year.[18] CA-MRSA typically causes skin infections, and 40 to 90% of CA-MRSA strains are accompanied by an exotoxin named Panton-Valentine leukocidin (PVL).[19] Regarding the molecular aspect,

HA-MRSA and CA-MRSA are distinguished by *mecA* types. The HA-MRSA usually presents *mecA* gene types I, II or III,[15] while the CA-MRSA regularly shows *mecA* gene types IV or V.[20] MRSA has been found in Thailand for more than 40 years.[21] Occasionally, MRSA outbreaks are incident, especially in hospitals.[22] MRSA possesses increased; risk factors enhancing MRSA prevalence are antibiotic use, prolonged hospitalization, intravascular intervention and hospitalization in an intensive care unit.[23] MRSA is usually spread by skin-to-skin contact. At-risk populations of MSRA carriers include groups such as dormitory dwellers, healthcare workers, military privates or conscripts, prisoners and those living in crowded conditions. Among healthcare workers (HCWs), the prevalence of MRSA nasal colonization has been estimated to be 4.6% in non-outbreak settings in Europe and the United States.[24] In Thailand, the prevalence of MRSA in HCWs was 1% to 7.36%.[25, 26] This MRSA colonization is potentially transmitted from HCWs to patients. It consequently causes serious problems with a significant concern of MRSA carriage among HCWs. The incidence of MSRA isolates from clinical specimens of Phramongkutklao Hospital has been increasing, including coagulase-negative staphylococci and *Escherichia coli*. Moreover, vancomycin-intermediate resistance *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA) have been reported in Thailand.[27,28] Routinely, MRSA screening among physicians and nurses of Phramongkutklao Hospital also revealed the continuous incidence of MRSA. However, an interesting group for screening MRSA comprised privates of the Medical Private Company, a group of HCWs working in the hospital. Thus, this study aimed to investigate the prevalence of MRSA nasal carriage, determine antibiotic resistance patterns in *S. aureus* isolates, and determine risk factors of *S. aureus* nasal carriages among privates of the Medical Private Company, Phramongkutklao Hospital.

Methods

Study design

A cross-sectional study was conducted to evaluate the prevalence of MRSA and *S. aureus* nasal carriage among privates of the Medical Private Company, Phramongkutklao Hospital. The study was approved by the Institutional Review Board (IRB), Royal Thai Army Medical Department (approval no. RF08_2555). Informed consent was obtained before collecting specimens. The study included 170 privates; the number of subjects was based on sample size calculation at a 95% reliability level using Yamane's formula.[29]

Sample collection

This study was conducted in the Medical Private Company of Phramongkutklao Hospital in 2015. The details of this study were informed to the subjects. A nasal swab was applied to collect specimens with a rotating technique neatly in both anterior nares of the subjects. All swabs were transported within Amies's transport media and then streaked on MRSA chromogenic agar and mannitol salt with egg-yolk agar, incubated at 35°C as a screening culture method. The bacterial growth was examined after 24 to 48 hours.

Isolation and identification

For all bacterial isolated colonies, macroscopic and microscopic examination using gram stain was performed for preliminary identification. All gram-positive cocci were confirmed by catalase test, and then all staphylococci were examined using the tube coagulase test. Furthermore, species were identified using the matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF). For staphylococci isolates, MRSA was detected using cefoxitin disk diffusion. Therefore, this study could also recover MRSE and MSSA as an outgrowth.

Molecular characterization for MRSA

The MRSA isolates were detected for the *mecA* gene using the Polymerase Chain Reaction (PCR). The isolates were inoculated in tryptic soy broth (TSB) at 35°C overnight. The culture was diluted

in 0.5 McFarland standards (approximately 1.5 x 10^8 CFU/mL) and extracted for DNA using the Pure-gene Yeast/Bact. Kit B (Qiagen, Germany). To detect the *mecA* gene, specific primers were used to amplify the 310-bp of the *mecA* gene according to a method described by McClure,[30] and SCC*mec* typing was determined by amplifying the *mec* and *ccr* gene complex.[31]

Antibiotic susceptibility pattern

According to the Clinical and Laboratory Standards Institute (CLSI) guidelines, all MRSA and MSSA isolates were tested for antibiotic susceptibility patterns, including cefoxitin, chloramphenicol, ciprofloxacin, clindamycin, erythromycin, fosfomycin, fusidic acid, gentamicin, linezolid, tetracycline and trimethoprim/sulfamethoxazole using the disk diffusion method of Kirby-Bauer according to CLSI guidelines.[32] *S. aureus* (ATCC29213) was the control strain used for the susceptibility test.

Questionnaire for risk factors

A questionnaire was provided to collect data from the subjects. Demographic data were collected, including age, sex, hometown and occupation, before entering the military draft. Behavioral data included handwashing habits with and without soap, bathing, utensil sharing, nose-picking, smoking and a history of alcohol consumption. Health data included a history of skin infection, previous hospitalization, underlying disease, antibiotic use within the last two months, and history of surgery. Finally, operations while working in the hospital included touching patients, touching medical equipment, glove-wearing and mask-wearing.

Statistical analysis

The *S. aureus* positive samples were statistically analyzed using the data of independent factors possibly contributing to *S. aureus* nasal carriage. The crude odds ratio (OR) was determined using bivariate analysis with 95% confidence intervals (CI). All *p*-values were two-sided, with a $p < 0.05$ considered a significant correlation. The statistically significant factors were analyzed for adjusted odds ratio (AOR) using Cochran's and Mantel-Haenszel's multiple logistic regression analysis. All analyses were performed using IBM SPSS, Version 22.0.

Results

Prevalence of MRSA, MSSA, MRSE and other staphylococci

A total of 185 isolates were recovered from 170 samples, of which 157 were staphylococci (92.35%), including 161 staphylococcal isolates. Of 157 samples, 27 were coagulase-positive staphylococci (CoPS) (15.88%), and 131 were coagulase-negative staphylococci (CoNS) (77.06%). Of 27 CoPS, 16 were *S. aureus* (9.41%), and 11 were for *S. intermedius* (6.47%). Of 16 samples of *S. aureus*, one was MRSA (0.59%), and 15 were MSSA (8.82%). Of 131 CoNS, 103 were *S. epidermidis* (60.59%), and 32 were other CoNS (18.82%). Of 103 samples of *S. epidermidis*, 2 were MRSE (1.18%), and 101 were methicillin-sensitive *S. epidermidis* (MSSE) (59.41%). The prevalence of MRSA, MSSA, and MRSE nasal carriage were 0.59, 8.82, and 1.18%, respectively (**Figure 1**).

Isolation of bacterial strain

Of 185 bacterial isolates, 12 species were confirmed using the MALDI-TOF. The predominant one was *S. epidermidis* (55.68%), followed by *Corynebacterium* sp. (8.65%), *S. aureus* (8.65%), *S. hominis* (8.11%), *S. intermedius* (5.95%), *S. warneri* (3.24%), *Micrococcus* sp. (2.70%) and *S. saccharolyticus* (2.16%). Others were *Corynebacterium accolens*, *S. capitis*, *S. caprae*, and *S.haemolyticus,* at 1.08% each (**Table 1).**

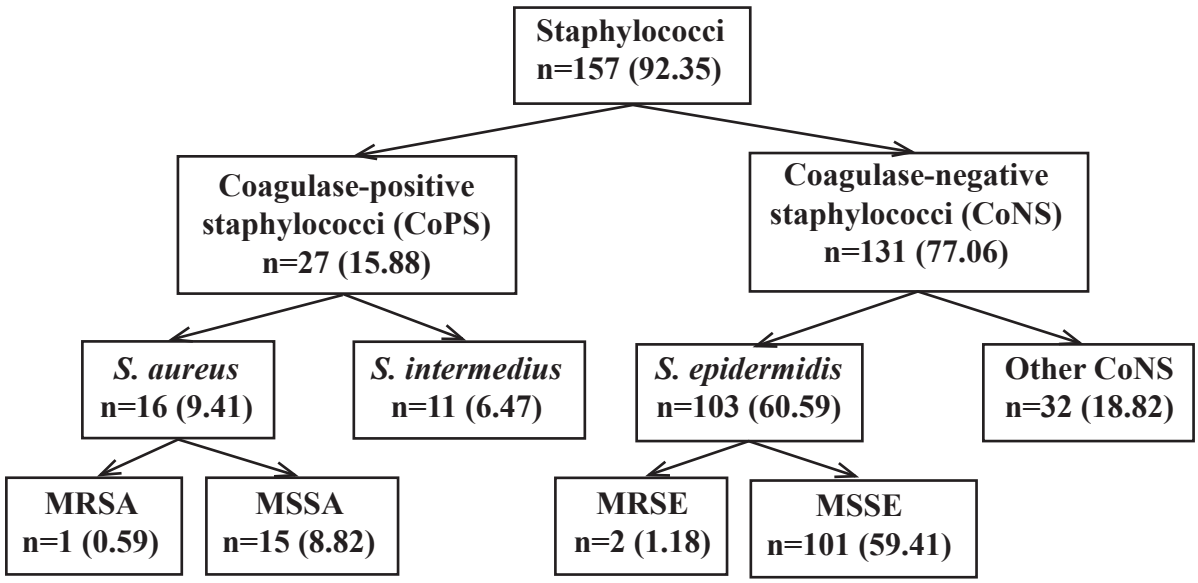

Figure 1. Prevalence of staphylococci nasal carriage among 170 privates of the Medical Private Company, Phramongkutklao Hospital

Table 1. Bacterial species were identified among 185 bacterial isolates from privates of the Medical Private Company, Phramongkutklao Hospital

Bacterial species	Number of isolates	%
Gram-positive cocci		
Staphylococci		
CoPS		
S. aureus	16	8.65
S. intermedius	11	5.95
CoNS		
S. epidermidis	103	55.68
S. hominis	15	8.11
S. warneri	6	3.24
S. saccharolyticus	4	2.16
S. capitis	2	1.08
S. caprae	2	1.08
S. haemolyticus	2	1.08
Micrococci		
Micrococcus sp.	5	2.70
Gram-positive bacilli		
Corynebacterium sp.	16	8.65
Corynebacterium accolens	2	1.08

Antibiotic susceptibility pattern for S. aureus

The cefoxitin disk diffusion test for the 16 isolates of *S. aureus* revealed that only one isolate was MRSA. The MRSA isolate showed resistance to ciprofloxacin, clindamycin, erythromycin, gentamicin and tetracycline. On the other hand, the isolate was susceptible to chloramphenicol, fosfomycin, fusidic acid, linezolid and trimethoprim/sulfamethoxazole. In addition, the MSSA isolates were 13.33% resistant to tetracycline. Nevertheless, the isolates were 100% susceptible to chloramphenicol, ciprofloxacin, clindamycin, erythromycin, fosfomycin, fusidic acid, gentamicin, linezolid, cefoxitin and trimethoprim/sulfamethoxazole.

MRSA genotyping

Of 185 isolates, only one isolate was suspected of MRSA by phenotypic investigation. The existence of the *mecA* and *ccrA2* genes in an MRSA isolate was observed. The SCC*mec* typing was SCC*mec* type II, as shown in **Table 2**.

Risk factors associated with S. aureus nasal carriage

A total of 170 subjects were privates, male, aged 20 to 23 years, and residing together in dormitories in a military camp of the Medical Private Company, Phramongkutklao Hospital. Using bivariate analysis, utensil sharing (OR: 3.92; 95% CI=1.21-12.72) and antibiotic use within the last two months (OR: 4.85; 95% CI=1.12-21.00) were significantly associated with *S. aureus* nasal carriage as shown in **Table 3**. However, using multiple logistic regression analysis, utensil sharing was independently associated with *S. aureus* nasal carriage (AOR= 4.41; 95% CI=1.33-14.61)

Table 2. PCR amplification of the *mecA* and *ccr* genes for SCC*mec* type using the MRSA isolate

Gene amplification	PCR	Result
mecA (310 bp)	Positive	Methicillin-resistant isolate
ccrA1 (415 bp)	Negative	
ccrA2 (937 bp)	Positive	Type II of SCC*mec*
ccrA3 (518 bp)	Negative	

Table 3. Bivariate analysis and multiple logistic regression analysis for possible factors associated with *S. aureus* nasal carriage

Factor	*S. aureus* nasal carriage (%)		Bivariate analysis		Multiple logistic regression analysis	
	positive (n=16)	negative (n=154)	OR (95%CI)	*p*-value	AOR (95%CI)	*p*-value
Personal behavior						
Handwashing	14 (87.50)	147 (95.45)	3.00 (0.57-15.85)	0.1958		
Handwashing with soap	15 (93.75)	145 (94.16)	1.07 (0.13-9.07)	0.9477		
Bathing habit at least twice/day	15 (93.75)	146 (94.81)	1.22 (0.14-10.40)	0.8578		
Utensil sharing	5 (31.25)	16 (10.39)	3.92 (1.21-12.72)	0.0229*	4.41 (1.33-14.61)	0.016*
Nose-picking	14 (87.50)	115 (74.68)	1.02 (0.31-3.34)	0.2667		
Smoking	13 (81.25)	105 (68.18)	2.02 (0.55-7.42)	0.2885		
Alcohol consumption	12 (75.00)	109 (70.78)	1.24 (0.38-4.05)	0.7232		

Table 3. Bivariate analysis and multiple logistic regression analysis for possible factors associated with *S. aureus* nasal carriage (Cont.)

Factor	*S. aureus* nasal carriage (%)		Bivariate analysis		Multiple logistic regression analysis	
	positive (n=16)	negative (n=154)	OR (95%CI)	*p*-value	AOR (95%CI)	*p*-value
Health information						
History of skin infection	3 (18.75)	17 (11.04)	1.86 (0.48-7.19)	0.3687		
Previous hospitalization	1 (6.25)	7 (4.55)	1.40 (0.16-12.16)	0.7603		
Underlying disease	1 (6.25)	13 (8.44)	0.72 (0.09-5.92)	0.7624		
Antibiotic use within the last two months	3 (18.75)	7 (4.55)	4.85 (1.12-21.00)	0.0349*	3.077 (0.85-18.07)	0.079
History of surgery	0 (0.00)	13 (8.44)	0.32 (0.02-5.60)	0.7840		
Operation in hospital						
Touching patients	1 (6.25)	12 (7.79)	0.79 (0.10-6.50)	0.8255		
Touching medical equipment	2 (12.50)	13 (8.44)	1.55 (0.32-7.57)	0.5886		
Glove-wearing	4 (25.00)	37 (24.03)	0.95 (0.29-3.12)	0.9309		
Mask-wearing	11 (68.75)	107 (69.48)	1.03 (0.34-3.14)	0.9519		

*Significantly different (*p*-value <0.05), OR: crude odds ratio, AOR: adjusted odds ratio, CI: confident interval

Discussion

This study showed a low prevalence (0.59%) of MRSA nasal carriage among privates working in the hospital, which was less than other studies. In this study, MRSA genotyping was performed using only the cefoxitin-resistant *S. aureus* isolates, which might have revealed less MRSA prevalence. In addition, PCR amplification of all *S. aureus* isolates would be very helpful in determining the true prevalence of MRSA nasal carriage. However, in this study, PCR was used only for bacterial genotyping. Many reports showed a high MRSA prevalence, ranging from 0.67 to 36.06% among healthcare workers. Most healthcare workers could have acquired MRSA after contact with MRSA-positive patients. [33, 34] In Thailand, related studies showed that the prevalence of MRSA nasal carriage was 1% among medical sciences students in the north [25] and 7.36% among medical students in the central region.[26] As mentioned, a wide range of prevalence could be due to different sensitivities of methods used for the study. For this reason, a study not recovering MRSA did not imply that MRSA would be absent. [35]

In this study, the risk factor constituted utensil sharing, similar to a related study in which risk factors for MRSA and *S. aureus* were personal hygiene, especially sharing items between household individuals.[36] These results support that this MRSA isolate was likely to be CAMRSA. However, the MRSA-positive subject confirmed the *mecA* DNA fragment[37] and SCC*mec* typing.[38] The result revealed type II of SCC*mec* at 937 bp of the *ccrA2* gene. Therefore, this MRSA isolate might be HA-MRSA which commonly carries SCC*mec* type II [18]. However, whole genome sequencing of the MRSA isolate should be further performed to distinguish between HA-MRSA and CA-MRSA.

For MSSA, our result was similar to related studies indicating 15.0 and 20.25%, respectively, the MSSA nasal colonization among medical science students and medical students.[25, 26] These data emphasized that the establishment of MSSA could be generally seen as nasal colonization among healthcare workers. Our result

showed 13.3% tetracycline-resistant MSSA isolates, differing from that of medical science students (23.3%).[39] MSSA from nasal colonization among medical science students resisted penicillin, clindamycin and erythromycin at 88.4, 39.5, and 37.2%, respectively, revealing higher resistance than our results. [39]

In this study, management of the private identified as the nasal carriage of MRSA was treated with the proper antibiotic. Methicillin-resistant horizontal transmission hypotheses suggested that MSSA obtained *mec*A DNA fragments transferred from MRSE or MRCoNS into itself and then became MRSA.[40] Our study also showed various species of CoNS indicating the potential for exchanging the *mecA* gene among staphylococcal species.

Conclusion

The study confirmed the existence of MRSA in a group of privates working as HCWs in a hospital. A risk factor of healthcare-associated MRSA was utensil sharing, likely to occur when they resided in the same accommodation. Therefore, infection control measures in hospitals should be realized for the transmission of MRSA, even from HCWs. However, MRSA screening would be more reliable when using molecular techniques for confirmation.

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