Prevalence and antibiotic sensitivity profiles of *Staphylococcus aureus* nasal carriage among preclinical and clinical medical students in a Malaysian university

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**ABSTRACT**

Aims: Prevalence of Methicillin-resistant *Staphylococcus aureus* (MRSA) strains in healthcare (HA-MRSA) and community (CA-MRSA) incurred costly morbidity and mortality. This study assessed the prevalence and antibiotic sensitivity profile of *S. aureus* and MRSA isolates from medical students.

Methodology and results: A cross-sectional study of nasal swabs from 60 medical students yielded 93% positive *S. aureus*. In this study, erythromycin, fusidic acid, gentamicin, penicillin, vancomycin and methicillin were used. The most significant antibiotic sensitivity against *S. aureus* was fusidic acid (p-value = 0.0042). The *S. aureus* and MRSA isolates from clinical students were more resistant than those of preclinical students against erythromycin (44%; 15%), fusidic acid (33.3%; 10%), penicillin (85%; 86.9%), vancomycin (11.1%; -) and methicillin (19.4%; 15%) respectively while the isolates from preclinical students were more resistant than those of clinical students against gentamicin (5%; -).

Conclusion, significance and impact of study: In this study, gender, age and duration of clinical exposure had no significant bearing on the prevalence of nasal *S. aureus* and MRSA respectively. No MRSA infections were detected in preclinical (15%) and clinical (19%) students positive for MRSA, suggesting that these students may be carriers of CA-MRSA. A larger study will be implemented to provide baseline data for monitoring CA-MRSA infections, genotyping and constructing of phylogenetic tree.

Keywords: Methicillin-resistant, *Staphylococcus aureus*, medical students, nasal

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**INTRODUCTION**

*Staphylococcus aureus* (*S. aureus*) is a Gram-positive bacteria, cluster-forming cocci and normal flora found on nasal passages, skin and mucous membranes of human. It is present in approximately 30% of healthy people population (von Eiff et al., 2001). Staphylococci, ubiquitous colonisers of human epithelia are implicated in soft tissue infections and invasive diseases namely osteomyelitis, necrotizing fasciitis, severe sepsis and endocarditis (Miller et al., 2005; Kleven, 2007). Methicillin-Resistant *Staphylococcus aureus* (MRSA) was first documented in 1960 (Barber, 1961) and classified into Hospital-acquired Methicillin-Resistant *Staphylococcus aureus* (HA-MRSA) and Community-acquired Methicillin-Resistant *Staphylococcus aureus* (CA-MRSA) (Naimi et al., 2003; Kluymans-Vandenbergh and Kluymans, 2006; David and Daum, 2010).

Previous studies had shown that developing countries for instance, Nigeria (14%), India (16%) and Malaysia (26%) had lesser *S. aureus* carriers than developed countries like United State (32%) and Netherlands (35%) (Kleven, 2007; Alvarez-Uria and Reddy, 2012; Al-Talib et al., 2013; Dulon et al., 2014). However, Asia is currently among the regions with the highest prevalence rates of HA-MRSA and CA-MRSA in the world (Song et al., 2011; Chen and Huang, 2014; You et al., 2017). Prevalence of HA-MRSA infections had been reported to be 70-80% in Asia region (Boucher and Corey, 2008; Song et al., 2011). While a study reported 7% of adults were carrying MRSA in their nasal passageway (Hidron et al., 2005), nasal carriage MRSA colonization rate was found higher in healthcare setting than in community (Berthelot et al., 2004; Trepanier et al., 2013; Dulon et al., 2014). Studies also suggested that healthy individual may act as medium that transferred MRSA among the communities causing an increase in MRSA infections (Kluymans-Vandenbergh and Kluymans, 2006; David and Daum, 2010; Conceicao et al., 2013; Conceicao et al., 2014). CA-MRSA showed high resistance against...
beta-lactam antibiotics, hence they were more difficult to treat (Kluytmans-Vandenbergh and Kluytmans, 2006). Conversely, HA-MRSA had better resistance against clindamycin and doxycycline than CA-MRSA (Alvarez-Uria and Reddy, 2012; Lim et al., 2013). Although CA-MRSA infections are usually mild, but once prolonged may be severe and requires hospitalization or even causes death. CA-MRSA had a larger spread to the community than HA-MRSA which was limited to the healthcare setting and easier to control since the strain can only be acquired and developed inside the hospital or due to healthcare facilities (Chen and Huang, 2014). Therefore, it is pertinent to assess the prevalence of MRSA, its strain, exposure to the community especially in Malaysia given the ease of traveling within the ASEAN regions and its antibiotic sensitivity profile to aid in reducing the morbidity and mortality MRSA may trigger.

MATERIALS AND METHODS

Study population

This was a cross-sectional study involving 24 preclinical and 36 clinical students from the Faculty of Medicine and Health Sciences (FMHS), Universiti Malaysia Sarawak (UNIMAS). These preclinical students had little or no patient encounters due to their lecture-based curriculum while clinical students were more involved in bedside learning. The study was approved by the Ethics Committee of the National Institute of Health (Ministry of Health) and Medical Ethical Committee, FMHS, UNIMAS.

Sampling

Nasal swab samples were collected and were kept at room temperature for 3 h before culturing and microbiology examinations were conducted. Primary culture was streaked on blood agar (OXOID, UK) (Figure 1) and mannitol salt agar (MSA) (OXOID, UK) (Figure 2) to culture and isolate bacteria. Microbiological tests for S. aureus including Gram-staining (HIMEDIA, India), catalase test (Sigma) and coagulase test (Sigma) were performed. Colony suspension in Mueller-Hinton (MH) broth (OXOID, UK) was obtained from single colony positive on MSA agar to create bacterial lawn on MH agar. Standard Antibiotic discs (OXOID, UK) namely Erythromycin (15 µg), Fusidic acid (10µg), Gentamicin (10 µg), Methicillin (5 µg), Penicillin (10µg) and Vancomycin (30 µg) were placed on the bacterial lawn. The agars were incubated for 24 h at 37 °C. Inhibition zones were measured and recorded (Figure 3) while in the absent of inhibition zone, the culture samples were identified as resistant against antibiotic of interest (Figure 4) The antibiotic sensitivity was interpreted using the antibiotic sensitivity chart provided by OXOID (Table 1). The final antibiotic resistance validation was done on Brilliance MRSA agar (ThermoFisher Scientific) (Figure 5).

Figure 1: Blood agar with presence of S. aureus. In the Blood Agar plate, most of the organisms appeared as colourless to yellowish-white colonies of various sizes (small, medium, big).

Figure 2: Mannitol salt agar (MSA) with growth of bacteria. Since S. aureus fermented mannitol, the presence of it was indicated by the changes of the MSA reddish colour into yellow.

Figure 3: Inhibition zone was measured and recorded. The smaller the inhibition zone, the more resistant the bacteria were towards the antibiotic of interest.
Of the positive previous findings (Chen et al., 2010), MRSA obtained from nasal swab samples yielded both S. aureus and MRSA from individuals. The antimicrobial sensitivity profiles of S. aureus samples (Table 3) from clinical students were found to be more resistant than preclinical students against erythromycin (29%; 5%), fusidic acid (21%; 4%), penicillin (57%; 30%), vancomycin (7%; -%) and methicillin (13%; 5%) respectively. On the contrary, the S. aureus samples from preclinical students were found to be more resistant than clinical students against gentamicin (0%; 2%). Overall, there was a significant difference between preclinical and clinical year students against fusidic acid (p= 0.042) while less significantly associated with erythromycin (p= 0.082), penicillin (p= 0.691), vancomycin (p= 0.218) and methicillin (p= 0.780). In this study, 93% of the samples collected were positive for S. aureus in contrast with previous studies conducted in West Malaysia at 26% and 28.7% and China at 46% respectively (Neela et al., 2010; Ma et al., 2011; Al-Talib et al., 2013). Of the positive S. aureus samples isolated, 17.8% of these were found to be MRSA based on antibiotic susceptibility test and growth on MRSA Brilliance agar. This result was lower than those reported in HUSM (21.5%) (Al-Talib et al., 2010; Al-Talib et al., 2013). This study also demonstrated no significant association between the duration of clinical exposure and the nasal carriage rate of S. aureus (p= <0.001), concurring with the previous findings (Chen et al., 2012). However, culture samples from the clinical students showed smaller inhibition zone than those of preclinical students. There was a statistically significance difference associated with fusidic acid (p= 0.0042) between preclinical and clinical medical students with 86% of fusidic acid resistant S. aureus contributed by clinical year students.

This study showed gender, age and duration of clinical exposure had no significant bearings on the prevalence of S. aureus and MRSA respectively. The results also demonstrated both clinical (19%) and preclinical students (15%) carried MRSA in their nares with the clinical students accorded a slightly higher prevalence. The results further suggested that these medical students may have CA-MRSA rather than HA-MRSA as the prevalence of MRSA in both cohorts of students were similar.

Table 1: Antibiotics sensitivity range as provided by OXOID, UK. This table summarized the standard antibiotic discs (µg) inhibition zone measurement (mm) of resistance (R), intermediate (I) and sensitive (S) based on their standard S. aureus from ATCC.

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Resistance (R)</th>
<th>Intermediate (I)</th>
<th>Sensitive (S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin</td>
<td>≤ 13</td>
<td>14 - 22</td>
<td>≥ 23</td>
</tr>
<tr>
<td>Fusidic Acid</td>
<td>≤ 18</td>
<td>17 - 20</td>
<td>≥ 21</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>12</td>
<td>13 - 14</td>
<td>15</td>
</tr>
<tr>
<td>Penicillin</td>
<td>≤ 28</td>
<td>-</td>
<td>≥ 29</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>≤ 9</td>
<td>10 - 11</td>
<td>≥ 12</td>
</tr>
<tr>
<td>Methicillin</td>
<td>≤ 9</td>
<td>10 - 13</td>
<td>≥ 14</td>
</tr>
</tbody>
</table>

RESULTS AND DISCUSSION

A total of 60 nasal swab samples were collected from 20 preclinical year students and 36 clinical year students respectively. From these samples, 56 students were positive for S. aureus while 4 samples collected from preclinical year students were negative for S. aureus (Table 2). Some of the nasal swab samples yielded both S. aureus and MRSA from individuals. The antimicrobial sensitivity profiles of S. aureus samples (Table 3) from clinical students were found to be more resistant than preclinical students against erythromycin (29%; 5%), fusidic acid (21%; 4%), penicillin (57%; 30%), vancomycin (7%; -%) and methicillin (13%; 5%) respectively. On the contrary, the S. aureus samples from preclinical students were found to be more resistant than clinical students against gentamicin (0%; 2%). Overall, there was a significant difference between preclinical and clinical year students against fusidic acid (p= 0.042) while less significantly associated with erythromycin (p= 0.082), penicillin (p= 0.691), vancomycin (p= 0.218) and methicillin (p= 0.780). In this study, 93% of the samples collected were positive for S. aureus in contrast with previous studies conducted in West Malaysia at 26% and 28.7% and China at 46% respectively (Neela et al., 2010; Ma et al., 2011; Al-Talib et al., 2013). Of the positive S. aureus samples isolated, 17.8% of these were found to be MRSA based on antibiotic susceptibility test and growth on MRSA Brilliance agar. This result was lower than those reported in HUSM (21.5%) (Al-Talib et al., 2010; Al-Talib et al., 2013). This study also demonstrated no significant association between the duration of clinical exposure and the nasal carriage rate of S. aureus (p= <0.001), concurring with the previous findings (Chen et al., 2012). However, culture samples from the clinical students showed smaller inhibition zone than those of preclinical students. There was a statistically significance difference associated with fusidic acid (p= 0.0042) between preclinical and clinical medical students with 86% of fusidic acid resistant S. aureus contributed by clinical year students.

This study showed gender, age and duration of clinical exposure had no significant bearings on the prevalence of S. aureus and MRSA respectively. The results also demonstrated both clinical (19%) and preclinical students (15%) carried MRSA in their nares with the clinical students accorded a slightly higher prevalence. The results further suggested that these medical students may have CA-MRSA rather than HA-MRSA as the prevalence of MRSA in both cohorts of students were similar.

Table 2: Staphylococcus aureus positive and S. aureus negative from nasal swab samples. A tabulated data of 2 cohorts of students, namely preclinical and clinical students and the prevalence of S. aureus in number and percentage with Chi-square and p-value.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>S. aureus positive n (%)</th>
<th>S. aureus negative n (%)</th>
<th>Chi-square value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical</td>
<td>20 (83.3)</td>
<td>4 (16.7)</td>
<td>38.57</td>
<td>&lt;0.001∗</td>
</tr>
<tr>
<td>Clinical</td>
<td>36 (100.0)</td>
<td>0 (0.0)</td>
<td>27.20</td>
<td>0.006</td>
</tr>
</tbody>
</table>

∗Fisher exact test
Table 3: Effects of antibiotic sensitivity on *S. aureus* cultured from preclinical and clinical students. A tabulated data depicting the different antibiotics (erythromycin, fusidic acid, gentamicin, penicillin, vancomycin and methicillin) of interest tested on nasal swab samples obtained from 24 preclinical and 36 clinical students respectively. The antibiotic profiles (sensitive, intermediate, resistant) were recorded and percentages were calculated with Chi-square values and p-values. Note: Some nasal samples from students yielded both *S. aureus* and MRSA.

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Year</th>
<th>Sensitive, n (%)</th>
<th>Intermediate, n (%)</th>
<th>Resistant, n (%)</th>
<th>Chi square value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin</td>
<td>Preclinical</td>
<td>14 (70.0)</td>
<td>3 (15.0)</td>
<td>3 (15.0)</td>
<td>5.01</td>
<td>0.082</td>
</tr>
<tr>
<td></td>
<td>Clinical</td>
<td>16 (44.4)</td>
<td>4 (11.1)</td>
<td>2 (10.0)</td>
<td>6.32</td>
<td>0.042</td>
</tr>
<tr>
<td>Fusidic acid</td>
<td>Preclinical</td>
<td>18 (90.0)</td>
<td>0 (0.0)</td>
<td>2 (10.0)</td>
<td>1.00</td>
<td>0.357</td>
</tr>
<tr>
<td></td>
<td>Clinical</td>
<td>31 (58.3)</td>
<td>3 (8.3)</td>
<td>12 (33.3)</td>
<td>0.67</td>
<td>0.691</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Preclinical</td>
<td>19 (95.0)</td>
<td>0 (0.0)</td>
<td>1 (5.0)</td>
<td>1.83</td>
<td>0.057</td>
</tr>
<tr>
<td></td>
<td>Clinical</td>
<td>36 (100.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>3.05</td>
<td>0.016</td>
</tr>
<tr>
<td>Penicillin</td>
<td>Preclinical</td>
<td>31 (15.0)</td>
<td>0 (0.0)</td>
<td>17 (85.0)</td>
<td>0.67</td>
<td>0.691</td>
</tr>
<tr>
<td></td>
<td>Clinical</td>
<td>4 (11.1)</td>
<td>0 (0.0)</td>
<td>32 (86.9)</td>
<td>3.05</td>
<td>0.016</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Preclinical</td>
<td>20 (100.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>3.05</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>Clinical</td>
<td>31 (86.1)</td>
<td>1 (2.8)</td>
<td>4 (11.1)</td>
<td>4.56</td>
<td>0.033</td>
</tr>
<tr>
<td>Methicillin</td>
<td>Preclinical</td>
<td>15 (75.0)</td>
<td>2 (10.0)</td>
<td>3 (15.0)</td>
<td>0.498</td>
<td>0.780</td>
</tr>
<tr>
<td></td>
<td>Clinical</td>
<td>27 (75.0)</td>
<td>2 (5.6)</td>
<td>7 (19.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Fisher’s exact test*

Albeit no significant association between the duration of clinical exposure and antibiotic susceptibility (p=0.873), the highest number of antibiotic resistant *S. aureus* was those of penicillin (preclinical: 85%; clinical: 86.9%) as also observed in other studies (Du et al., 2011; Syafinaz et al., 2012). In this study, the most sensitive antibiotic was vancomycin (preclinical: 100%; clinical: 86.1%) as observed by other researchers (Onanuga and Temedie, 2011; Syafinaz et al., 2012) and 31.6% of the SA isolated were resistant against macrolide erythromycin. Due to the relatively small sample size, the risk factors for the acquisition of MRSA among the medical students in current study could not be identified. It was noted that there was a slight indication of a change in pattern of *S. aureus* nasal carriage, but a bigger sample size would be needed to provide a sound analysis.

CONCLUSION

This study demonstrated the high prevalence of *S. aureus* nasal carriage among these 60 medical students, indicative of a probable change in *S. aureus* nasal carriage pattern. While MRSA nasal colonization among these students was low, penicillin-resistant *S. aureus* was prevalent. We suggest a larger sample size study in different medical schools and hospitals to provide essential epidemiological information on MRSA in healthcare settings.

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