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Original Article

Sequence types 8, 59, and 45 methicillin resistant *Staphylococcus aureus* as the predominant strains causing skin and soft tissue infections in Taiwan's prisons and jails

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Abstract *Background:* Methicillin-resistant *Staphylococcus aureus* (MRSA) is the predominant cause of skin and soft tissue infections (SSTIs), which is a problem in prisons and jails. We conducted this study to understand MRSA molecular characteristics among inmates with SSTIs, and we chose MRSA isolates from a community hospital as a comparison.
Methods: A total of 219 MRSA isolates from three custodial facilities and 134 isolates from a community hospital in Taiwan were collected in the 2017 calendar year. MRSA isolates were investigated molecularly by staphylococcal chromosome cassette *mec* (SCC*mec*) type, mupirocin, and chlorhexidine genotypical resistance, and multi-locus sequence typing (ST).
Results: Of the 219 MRSA isolates from custodial facilities, SCC*mec* IV was the most prevalent type (65.3%), followed by type V_T (32.4%) and type V (1.8%). Regarding sequence types, ST59 (36.4%), 8 (35.3%), and 45 (17.9%) were the leading three predominant types out of 184 selected MRSA isolates, and ST45 MRSA was more prevalent in custodial facilities ($p = 0.019$). The antimicrobial resistance rates varied for different MRSA strains, with ST45 MRSA having the lowest rates of resistance to most antimicrobials. Overall, 91.5% of isolates carried *mupA* gene and 25.8% were positive for *qacA/B* gene, this was independent of the MRSA sequence types.
Conclusions: ST59, ST8, and ST45 MRSA are the leading three MRSA strains causing SSTIs in Taiwan, 2017, but the molecular distribution varied distinctly between the custodial facilities and hospital settings. The genotypical mupirocin resistance rate is quite high in this study. The

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frequency of chlorhexidine resistance gene is relatively low, especially in MRSA isolates from custodial facilities.

Introduction

Since the emergence and wide spread of community acquired methicillin resistant *Staphylococcus aureus* (MRSA) in the 1990s, it has been the predominant cause of skin and soft tissue infections (SSTIs) and causes various clinical presentations such as folliculitis, furuncles, abscess, cellulitis, and necrotizing fasciitis etc. MRSA is not only problematic for general and hospitalized populations, but also for congregate populations.[1–5]

Outbreaks of MRSA SSTIs in custodial facilities, alongside the high rate of MRSA colonization rate and recurrent MRSA infections in inmates, have been widely reported in previous studies.[3–5] Although numerous studies have demonstrated distinct molecular epidemiological characteristics of MRSA in the community and hospitals,[6,7] only a limit number of studies have been conducted in correctional facilities, mostly in the Unites States.[3–5,8] In the Unites States, a high rate of MRSA colonization and SSTIs has been well documented in the incarcerated population. USA300 MRSA is not only the predominant strain in the community, but also accounts for almost 100% of MRSA SSTIs in prisons and jails.[3–5,8,9]

MRSA has been a notorious pathogen in Taiwan, too; however, the information on MRSA infections in custodial facilities is scarce. Chang Bing Show Chwan Memorial Hospital is a 768-bed community-based hospital and has been responsible for providing healthcare to three custodial facilities in Changhua, Taiwan (one prison, one jail and one rehabilitation unit) since 2017. Our study objectives in this study were to determine the prevalence of MRSA SSTIs in these custodial facilities, delineate the molecular characteristics and antimicrobial resistance of MRSA isolates from inmates and detainees, with a particular focus on mupirocin and chlorhexidine genotypic resistance, and compared these isolates to MRSA isolates from our hospital during the same study period.

Materials and methods

Study design and clinical MRSA isolates

In 2017, 280 and 771 non-duplicate pus/wound samples derived from SSTIs were collected from three custodial facilities and Chang Bing Show Chwan Memorial Hospital (CBSHMH), respectively. MRSA was isolated from 78.2% (219/280) of the samples from custodial facilities and from 17.3% (134/771) of the samples from CBSHMH. All 353 MRSA isolates were re-confirmed using coagulase testing, and cefoxitin susceptibility was assessed using the disc diffusion method according to the guideline of the Clinical and Laboratory Standard Institute before further molecular analysis. The informed consent requirement was waived owing to the retrospective nature of this study and because of no additional acquisition of personal medical information.

Genomic DNA extraction

Total DNA extraction was performed using the QIAamp Blood DNA Mini Kit (Qiagen, USA) in accordance with the manufacturer's instructions. Extracted DNA was stored at −80 °C before molecular genotyping.

Molecular genotyping

All MRSA isolates were tested for the staphylococcal cassette chromosome *mec* (SCC*mec*) type, which was determined by multiplex polymerase chain reactions (PCR), as described previously[10]; if this method failed to identify a particular type, another multiplex PCR strategy was applied.[11] Control strains for SCC*mec* types I, II, III, IVa and V_T were as follows: type I, NCTC10442; type II, N315; type III, 85/2082; and type IVa, JCSC4744, and type V_T, TSGH-17.

Multi-locus sequence typing (MLST) was performed on a fixed proportion of isolates for each representative SCC*mec* type. Seven housekeeping genes (*arc, aroE, glp, gmk, pta, tpi, and yqiL*) of *S. aureus* were used for MLST. Amplification of a portion of each gene was performed as described previously.[12] The amplified products were sequenced, and the sequences thus obtained were analyzed using software available at https://pubmlst.org/organisms/staphylococcus-aureus. A phylogenetic tree was constructed using neighbor-joining method with PHYLOViZ 2.0 software.

Antimicrobial susceptibility tests

For each MRSA isolate, antimicrobial susceptibility to 10 antibiotics, comprising oxacillin, penicillin, trimethoprim/sulfamethoxazole, levofloxacin, clindamycin, erythromycin, gentamicin, fusidic acid, teicoplanin, and linezolid, was tested using the microdilution methods (BD Phoenix PMIC/ID 50, version 6.21A/6.35A) in accordance with 2017 guideline of the Clinical and Laboratory Standard Institute.

Mupirocin and chlorhexidine genotypic resistance

All 353 MRSA isolates were genotypically tested for high-level resistance to mupirocin and chlorhexidine by using TaqMan-based real time PCR. Real time PCR was conducted using the ABI 7500 fast system, and the PCR primers and probes, which targeted *mupA* gene and *qacA/B* gene,[13] respectively, used have been previously reported. Target sequence amplification thermal cycle was performed as

follows: initial denaturation step at 95 °C for 10 min, followed by 40 cycles of 95 °C for 15 s and 56 °C for 60 s. Cycles over 35 were considered as negative.

Statistical analysis

All statistical analyses were performed using SPSS software (PAWS Statistics 18.0.0; IBM Corporation, Somers, NY, USA). Categorical variables were compared using Fisher's exact test or Pearson's chi-square tests, as appropriate. All comparisons were two-tailed, and *p* values of less than 0.05 were considered statistically significant.

Results

Molecular genotypes of clinical MRSA isolates

The SCC*mec* type and sequence type distribution of MRSA from custodial facilities and the hospital are presented in Fig. 1. Of the 219 MRSA isolates from custodial facilities, type IV was the most prevalent type (143, 65.3%), followed by type V_T (71, 32.4%) and type V (4, 1.8%). Of the 134 MRSA isolates from CBSHMH, the SCC*mec* type distribution was as follows: type IV (65, 48.5%), type V_T (41, 30.6%) and type V (22, 16.4%), respectively. On comparison of the SCC*mec* type distribution between custodial facilities and the hospital, only the proportion of MRSA type IV was significantly higher in custodial facilities (65.3% vs 48.5%, $p = 0.00072$).

In the present study, we selected 184 isolates accordingly for MLST typing, comprising 112 and 72 from custodial facilities and the hospital, respectively. Overall, ST59 MRSA was the predominant strain (36.4%) in this study, followed by ST8 (35.3%) and ST45 (17.9%). The most common combinations of sequence and SCC*mec* type found were ST59-MRSA-V_T (64, 34.8%), ST8-MRSA-IV (56, 30.4%) and ST45-MRSA-IV (16.3%). Fig. 1B presents the distribution of the MLST type in two study sites; ST45-MRSA was more prevalent in custodial facilities (23.2% vs 9.7%, $p = 0.019$), and no significant difference was noted among other sequence types. The constructed phylogenetic tree is illustrated in Fig. 2 and comprises five clonal complexes (CCs): CC8 (74, 40.2%), CC59 (68, 37.4%), CC45 (33, 17.9%), CC30 (5, 5.4%), and CC398 (4, 2.2%).

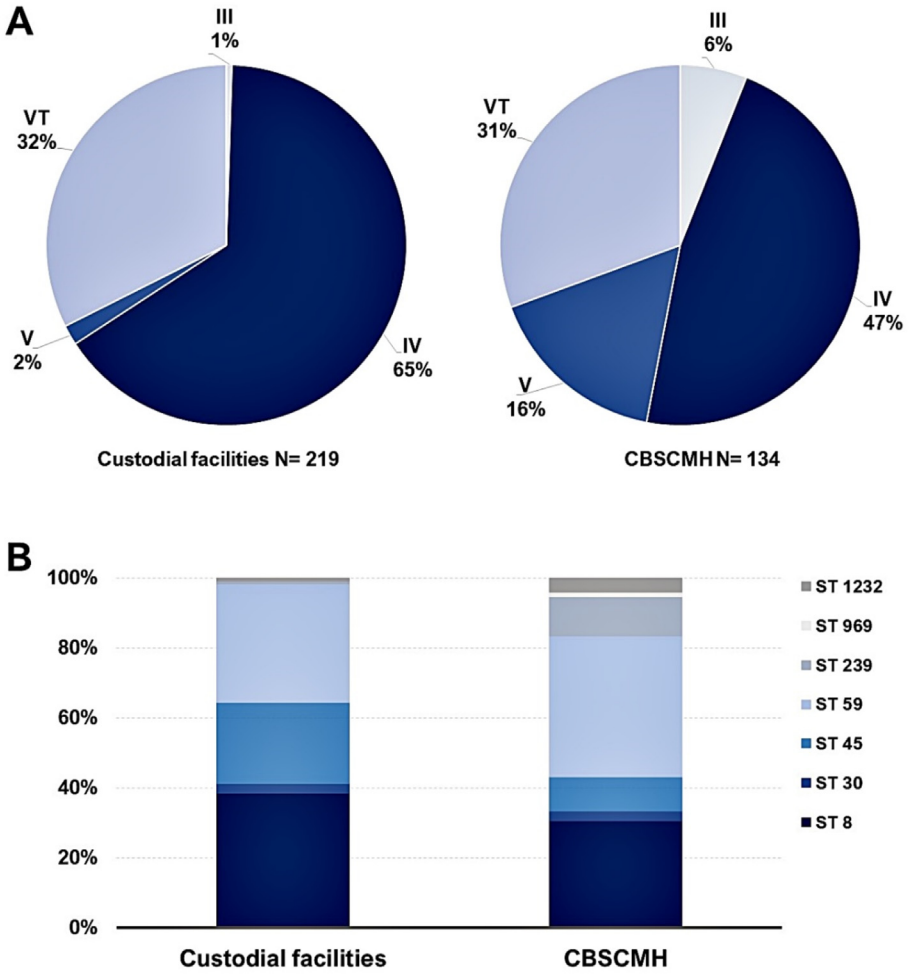

Figure 1. The distribution of methicillin-resistant *Staphylococcus aureus* (MRSA) staphylococcal cassette chromosome (SCC*mec*) types (A) and sequence types (B) by study sites. Compared with hospital MRSA isolates, there was a distinct molecular epidemiological pattern of MRSA isolates in custodial facilities, and the prevalence of ST45 MRSA was significantly higher in custodial facilities.

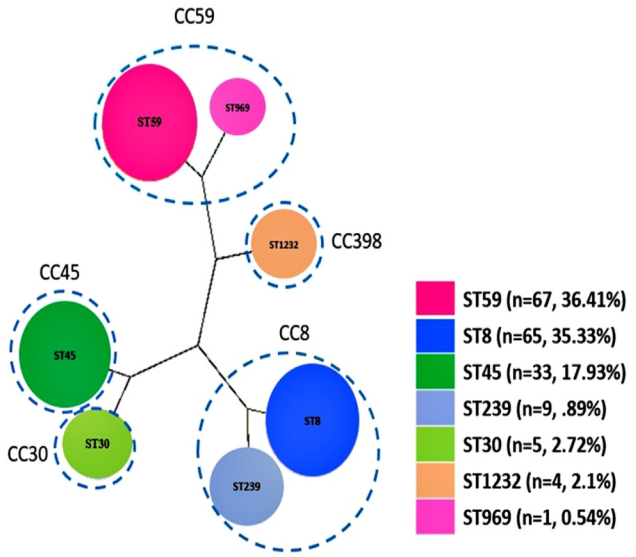

Figure 2. A phylogenetic tree was constructed using the neighbor-joining method on the basis of sequence types. Five major MRSA clones in this study were identified: CC8, CC45, CC59, CC30, and CC398.

Antibiogram of MRSA isolates

Of the 353 MRSA isolates, a high resistance rates to erythromycin (85.2%), clindamycin (68.8%), and levofloxacin (42.2%) were observed, wherase resistance rates to trimethroprim/salfamethoxazole and doxycycline were as low as 18.4% and 0.56%, respectively. Resistance to vancomycin, teicoplanin, or linezolid was not detected. The antimicrobial resistance rates were comparable across the two study sites (Table 1), however, significant differences were observed in antimicrobial resistance depending on the MRSA sequence type (Table 2).

Mupirocin and chlorhexidine genotypic resistance

The distribution of the genotypic resistance of 353 isolates to mupirocin and chlorhexidine is shown in Table 1 and is categorized by the study site. In general, the carriage rate of the high-level mupirocin resistance gene (*mup*A) was high (323/353, 91.5%), with it being detected at a higher rate in isolates from custodial facilities than in those from the hospital (95.4% vs 85.1%, $p = 0.0007$). The overall frequency of chlorhexidine genotypic resistance (*qac*A/B) was 25.8% (91/353), but a significant difference was found between the two study sites: 7.8% of custody isolates and 55.2% of hospital isolates ($p < 0.001$). In Table 3, we compared the relationship between mupirocin and chlorhexidine genotypic resistance and their distribution by each SCC*mec* type. Only 14 out of the 353 MRSA isolates were negative for *mup*A and *qac*A/B genes, and 75 of 91 (82.4%) MRSA isolates carried *qac*A/B gene concomitantly with *mup*A ($p = 0.0003$). Regarding chlorhexidine resistance by the SCC*mec* type, 100% of MRSA type III was genotypically resistant to chlorhexidine genotypically (9/9); whereas the carriage rate of *qac*A/B gene did not differ among other SCC*mec* and sequence types (Tables 2 and 3).

Discussion

In the present study, the prevalence rate of MRSA SSTIs in Taiwan's custodial facilities was 78.2%, which is in line with previous reports.[3–5,8,9,14] In the Unites States, the prevalence of MRSA SSTIs in custodial facilities dramatically increased from 10.5% to 86% in the recent decades.[3,4,14] Custodial populations are susceptible to contract MRSA infection because of overcrowding, poor personal hygiene, low education status, repeated incarcerations, high colonization rate, and intravenous drug users (IDU).[4,5,9] This highlights the importance of controlling MRSA transmission and infection in such congregate environments.

Regarding the MRSA sequence type, ST8 MRSA (USA300, CA-MRSA clone in North America) is the single predominant MRSA strain in USA prisons.[3,9] The present study revealed that three MRSA strains, namely ST59, ST8 and ST45 MRSA, are circulating in custodial facilities and in the community, which are different from those reports from the United States. ST59 MRSA is a well-known CA-MRSA Taiwan clone, which commonly carries SCC*mec* type V or V_T, and has been responsible for the majority of community associated MRSA infection in Taiwan for years.[6,7,15,16] ST59 MRSA has surpassed ST239 MRSA, which was the traditional hospital associated MRSA clone in Taiwan, and to become the

Table 1 Comparison of methicillin-resistant *Staphylococcus aureus* antimicrobial resistance rate between two study sites.

Parameter	Custodial facilities No. (%) (n = 219)	CBSHMH No. (%) (n = 134)	*p* value[a]
Resistance genes distribution			
mupA	209 (95.4)	114 (85.1)	0.0007
qacA/B	17 (7.8)	74 (55.2)	<0.001
Antimicrobial resistance rate			
Erythromycin	178 (81.3)	123 (91.8)	0.006
Clindamycin	145 (66.2)	98 (73.1)	0.172
Sulfamethoxazole/trimethoprim	50 (22.8)	15 (11.2)	0.006
Tetracycline	47 (21.5)	42 (31.3)	0.037
Levofloxacin	95 (43.4)	54 (40.3)	0.569
Doxycycline	0	2 (1.5)	0.069

[a] Chi-square test.

Table 2 Comparison of antimicrobial resistance rate between three major sequence types of methicillin-resistant *Staphylococcus aureus*.

Antibiotics	MRSA[b]				
	ST 8 (n = 65)	ST 45 (n = 33)	ST 59 (n = 67)	*p1*[a]	*p2*[a]
mupA	61 (93.8)	32 (97)	61 (91)	0.5	0.27
qacA/B	14 (21.5)	7 (21.2)	15 (22.4)	0.9	0.89
Erythromycin	63 (96.9)	7 (21.2)	65 (97)	0.97	<0.001
Clindamycin	33 (50.8)	7 (21.2)	65 (97)	<0.001	<0.001
Sulfamethoxazole/trimethoprim	1 (1.5)	0	25 (37.3)	<0.001	<0.001
Tetracycline	1 (1.5)	27 (81.8)	8 (11.9)	0.017	<0.001
Levofloxacin	62 (95.4)	5 (15.2)	0	<0.001	0.001
Doxycycline	0	0	0	0	0

[a] Chi-square test and ST 59 was used as reference for comparison. p1: ST8 vs.ST59 and p2: ST45 vs ST59.
[b] Data are depicted as isolate number and percentage (n, %).

predominant MRSA strain in hospitals.[7] By contrast, the distribution of ST8 MRSA was scattered in Taiwan before 2015.[7,16] A study of 5308 MRSA isolates collected between 1995 and 2015 in Taiwan detected ST8 MRSA in only 25 isolates (0.51%). The first isolate was identified in 2005, and the other 23 isolates have been collected since 2010.[17] This evidence reveals that ST8 MRSA had already existed in Taiwan for >10 years. Notably, the reported rate of ST8 MRSA has increased from <3% to 20.8% in Taiwan since 2016 [15,18], and our study found that ST8 MRSA accounts for 35.3% of 183 selected MRSA isolates. Moreover, ST 8 MRSA was the predominant MRSA stain in Taiwan's custodial facilities and has become the second major MRSA strain in the general population. The further spread of ST8 MRSA in the future is a concern in Taiwan.

In this study, the significantly higher proportion of ST45 MRSA in custodial facilities reflects another unique feature of the custodial population. ST45 MRSA has emerged in nursing homes and long-term care facilities in Taiwan and accounts for 19.7%–50% of MRSA colonization among residents in these facilities.[2,18,19] Our previous study found that, after ST59 MRSA, ST45 MRSA is the second leading strain colonizing the nares in the general population and in healthcare workers.[16] It is unclear why ST45 MRSA is highly prevalent in Taiwan's custodial facilities. Intravenous drug users are susceptible to MRSA colonization and contract MRSA SSTIs and invasive infections.[20,21] A Zurich study showed the spread of ST45 MRSA among intravenous drug users,[22] and 38.1% of Taiwan's custodial population are intravenous drug users.

Regarding antimicrobial resistance, the ST59 MRSA Taiwan clone typically presents with high resistance to erythromycin, tetracycline, levofloxacin, or ciprofloxacin but sensitive to doxycycline and sulfamethoxazole/trimethoprim.[2,6,7] However, it is concerning that the resistance rate to sulfamethoxazole/trimethoprim of ST59 MRSA in this study was unexpectedly higher than in previous studies. We cannot be sure the exact contributing reasons, but one study from a single medical center in Northern Taiwan has reported 34.7% of ST59 MRSA resistant to sulfamethoxazole/trimethoprim.[23] By contrast, ST 59 MRSA strains in this study showed low rates of resistance to tetracycline and levofloxacin. ST45 MRSA in Taiwan generally was less resistant to erythromycin, clindamycin, and doxycycline,[2,19] whilst ST45 MRSA strains in this study were highly resistant to tetracycline. Of note, ST8 MRSA strains in our study were extremely resistant to erythromycin and levofloxacin. More large-scale and multi-facets investigations are mandatory to clarify these findings. Chlorhexidine is a widely used biocide agent for environmental cleaning and decolonization. The MRSA resistance to chlorhexidine is mediated by the presence of several efflux mediated genes, especially *qac*A/B and *smr* genes.[24] The acquisition rate of *qac*A/B among MRSA strains varied widely: 2.2% in Spain,[25] 0.6%–7.1% in the USA,[26,27] and 28.9% in South Korean.[28] In Taiwan, several studies have screened MRSA isolates from single or multiple hospitals during different study periods and have shown that chlorhexidine genotypic resistance rate ranged from 35.4% to 55.4%.[23,29] Our study showed the consistent finding that 55.2% of hospital MRSA isolates harbored *qac*A/B gene. This high genotypic resistance rate might be due to the wide use of chlorhexidine in hospital setting.[23] Our study and the study by Sheng et al. all showed that ST239 MRSA isolates were the most resistant to both chlorhexidine and other antimicrobial agents.[29] Instead of the high genotypical resistance rate to mupirocin, only 7.8% of MRSA isolates from custodial facilities carried *qac*A/B gene, which

Table 3 Relationship between chlorhexidine and mupirocin genotypic resistance and distribution in each Staphylococcal cassette chromosome (SCC*mec*) types.

Parameter	*qacA/B* (+) (n = 91)	*qacA/B* (−) (n = 262)	*p* value[a]
mupA Gene			
mupA (+)	75 (82.4)	248 (94.7)	0.0003
mupA (−)	16 (17.6)	14 (5.3)	
SCC*mec* type			
III	9 (9.9)	0	<0.001
IV	51 (56)	155 (59.2)	0.6
V	7 (7.7)	18 (6.9)	0.79
V_T	24 (26.4)	88 (33.6)	0.2

[a] Chi-square test.

implicated the potential advantage of chlorhexidine use to mitigate the MRSA burden in Taiwan's custodial facilities.

High-level mupirocin resistance is mostly conferred by the plasmid-borne gene *mup*A, which produces a "eukaryotic-like" tRNA synthetase with no affinity for mupirocin. Two MRSA decolonization studies in the Unites States showed that 6.9%—7.5% of MRSA isolates were mupirocin-resistant, which were confirmed phenotypically and genotypically.[26,27] In Spain, high level mupirocin resistance was identified in 10.9% of blood MRSA isolates and all isolates carried the *mup*A gene.[25] Before 2010, no mupirocin phenotypic resistant MRSA was reported in Taiwan.[30] However, >90% of MRSA isolates in our study harbored *mup*A, even though mupirocin is not routinely used for MRSA decolonization in Taiwan. This finding is concerning and warrants a large-scale investigation.

There are two limitations of this study: first, even with the notice of the rising epidemiology of ST8 MRSA in this present study, we still cannot make sure these ST8 MRSA isolates are equal to USA 300 strain because of lacking evidence of pulse-field gel electrophoresis and the related molecular markers. Second, we did not test mupirocin and chlorhexidine phenotypical susceptibility on these MRSA isolates.

In conclusion, the MRSA molecular epidemiology is distinct between Taiwan's custodial facilities and the general population. ST8, ST59, and ST45 MRSA were three main MRSA stains causing SSTIs in Taiwan's custodial facilities. Moreover, the increasing emergence of ST8 and ST45 MRSA in Taiwan should be monitored. Resistance to Mupirocin, which is not used for MRSA decolonization in Taiwan, was high in this study. Finally, chlorhexidine may be a promising option to control MRSA spreading in custodial facilities.

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