Methicillin-resistant *Staphylococcus aureus* nasal carriage among patients receiving hemodialysis: comparison between a local hospital and a medical center in Taiwan

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Running title: MRSA among patients receiving hemodialysis in Taiwan

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Abstract

Background: *Staphylococcus aureus*, particularly methicillin resistant (MRSA), is a common pathogen among patients receiving hemodialysis. To understand MRSA carriage rate among these patients in different hospital levels, we conducted this study.

Materials and Methods: From January 2011 to June 2011, two nasal samplings with a 3-month interval were obtained from 161 patients (totally 265 samplings, both surveys for 104 patients) who undergoing hemodialysis in a medical center, and 135 patients (totally 264 samplings, both surveys for 129 patients) in a local hospital in Taiwan and sent for the detection of MRSA. Once MRSA carriage was identified, decolonization procedures were administered. All 161 patients in the medical center were observed if MRSA infections occurred during the study period.

Results: In the first sampling, the nasal MRSA colonization rate was 2.3% for the local hospital and 5.2% for the medical center. In the second sampling, the colonization rate was 4.4% and 3.4%, respectively. No significant difference was found between both hospitals, as well as both batches in term of nasal MRSA carriage rate. No significant associated risk factor for MRSA carriage was identified, either. 16 (80%) of the 20 MRSA isolates carried either type IV or V_T staphylococcal chromosome cassette (SCC*mec*) and 14 isolates were local community strains, belonging to sequencing type 59 linage. One colonized patient failed decolonization after the first sampling but was successfully decolonized after second sampling; others were successfully decolonized. Within the 6-month study period, two patients (1.24%) in the

medical center, one with MRSA colonization (9.1%), developed MRSA infection.

Conclusion: A substantial proportion of patients receiving hemodialysis in Taiwan had MRSA colonization, mostly community strains, but no additional risk factors for MRSA acquisition was identified. The carriage rate was no significant difference between those in the medical center and local hospital.

Key words: methicillin-resistant *Staphylococcus aureus*, nasal colonization, hemodialysis, decolonization, Taiwan

Introduction

Among patients with end-stage renal disease(ESRD), infection is the major cause of morbidity and modality during receiving hemodialysis[1]. One of the most common pathogens is *Staphylococcus aureus* (*S. aureus*)[2, 3].This population of hemodialysis patients has a significantly higher risk (relative risk=257) than the normal population of invasive Staphylococcal infection[4], such as infective endocarditis[5].

Anterior nares are the most important *S. aureus* reservoirs [6]which lead to subsequent clinical infection[7, 8]. In a prior study, methicillin-resistant *S. aureus*(MRSA) isolates are identified from 25% clinical *S. aureus* isolates from 25 hospitals in Europe[9].MRSA infection are associated with a high economic consequence and high mortality rate[10]. In a German study, clinical costs were much higher for MRSA infection than methicillin-susceptible *S. aureus* (MSSA) infection[11]. For monitoring MRSA infection, understanding MRSA carriage rate among patients receiving hemodialysis is important. Referring to hemodialysis, patients receiving this therapy have frequent contact to healthcare facilities and high frequency of indwelling catheter usage. We wondered if the population of patients undergoing hemodialysis has higher prevalence rate. In addition, no comparison has been done between out-patient hemodialysis clinics at different hospital levels in Taiwan. Hence, we conducted this research at a local hospital and a medical center.

As stated by former researches, MRSA strains are defined as two groups by their properties[12]. For example, community-associated(CA)- MRSA is

usually characterized as less resistance than healthcare-associated(HA)-MRSA. In addition, CA-MRSA and HA-MRSA possess different molecular features [13-15]. The transmission of CA-MRSA clones to healthcare facilities was reported at hospitals not only in U.S.A[16, 17]. but in Taiwan[14]. One of the aims of this study was to determine the epidemiology of MRSA isolates among hemodialysis patients.

Eradication of MRSA colonization has been well discussed, while bathing with clorhexidine in combination with mupirocin was suggested previously.[18-20] Since widely used of eradicative agents, resistance was noted by some authors[21, 22]. For this reason, clinical effectiveness of decolonization for hemodialysis patients was monitored in this research as well.

Material and method

Patient population This study was conducted in two hospital-based outpatient hemodialysis clinics at Chang Gung Memorial Hospital (CGMH) and Yang Ming Hospital (YMH) from Jan. 2011 to June 2011. CGMH and YMH are in northern Taiwan, and belonging to a tertiary medical center with 51 beds in outpatient hemodialysis clinic and a primary hospital with 36 beds in outpatient hemodialysis clinic, respectively. In January 2011, we invited 290 and 150 patients who receiving maintenance hemodialysis at CGMH and YMH respectively to participate this research. Within this 6-month studying periods, sampling was done twice in Jan. and Mar. Follow-up with the patients continued until June 30th 2011. All 161 patients in the medical center were

observed if MRSA infections occurred during the study period. This study was approved by the Institutional Review Board of CGMH.

Data collection To identify the potential risk factors for MRSA acquisition, following medical data were collected from medical records at two hospitals: demographics, underlying disease, latest hospitalization, length of time on hemodialysis, blood access of dialysis(Hickman, ateriovenous fistula, Gortex), previous S. aureus infection, and using of other catheters(Foley and tracheostomy tube).

Microbiologic methods Each nasal swab was circled in the anterior 1 cm of the nasal vestibular of both of participant's nares after written consents were obtained. The samples, then, were placed into the transport medium (Venturi Transystem, Copan Innovation Ltd.) immediately. Swab samples were inoculated by streak plate method onto Trypticase soy agar with 5% sheep blood plates. Those plates were incubated at 37 degree Celsius overnight. Identification of *S. aureus* was done by conducting morphology, gram stain, and coagulase tests of strains grown on agar plates. To identify MRSA clones, oxicillin disk was used by disk-diffusion method according to the recommendation of Clinical and Laboratory Standard Institute[23].

Antimicrobial susceptibility study The antimicrobial susceptibility of 10 antibiotics (Oxacillin, trimethoprim/sulfamethoxazole, penicillin, teicoplanin, linezolid, clindamycin, doxycyclin, fusidic acid, vancomycin, and erythromycin) was tested in accordance with the guideline of Clinical and Laboratory Standard Institute[23] by using the disk-diffusion method.

Molecular characteristics Colonized isolates of MRSA were molecularly characterized. The molecular methods used as typing of MRSA included pulsed-field gel electrophoresis (PFGE) with *Sma*I digestion, staphylococcal chromosomal cassette *mec* (SCC*mec*) typing, multilocus sequence type (MLST), and *spa* gene typing. In addition, the presence of Panton-Valentine leukocidin (PVL) genes was also examined. The detail of those procedures was described elsewhere.(Multiplex PCR for SCC*mec* type was performed according to the methods of Yoko Kondo et al. in 2007[24]; *spa* gene typing of Dag Harmsen et al., 2003[25]; Panton-Valentine leukocidine(PVL)gene of Gerard Lina et al., 1999[26]) The genotypes of PFGE were designate as in our previous studies according to the procedure described previously[27]. PFGE patterns were defined as subtypes when it appealed with fewer than four band differences from and existing genotype. MLST was examined for selective strains of representative PFGE patterns in accordance with the methods of Mark C. Enright et al. in 1999[28].

Intervention According to previous researches[19, 20], mupirocin ointment and chlorhexidine shampoo were used for nasal and skin decolonization. Mupirocin ointment was applied twice a day and chlorhexidine shampoo was used once a day by patient with MRSA colonization, and the decolonization period was five days. After the decolonization period, samples from patient's anterior nares were obtained again in one week for following-up.

Statistical analysis Comparing MRSA colonization between two hospitals was done using Pearson's chi-square tests. Continuous variables were compared between patients with MRSA colonization verses patients

without MRSA colonization using Student *t* test. The categorical variables were analyzed by chi-square test or Fisher's exact test, as appropriate. Odd ratios (ORs) were also calculated with 95% confidence intervals (CIs). The definition of statistical significance was $p < 0.05$. For statistical analysis, SPSS 17.0 software was used.

Results

Between January to June 2011, sampling was done twice, and a total of 529 (265 at CGMH and 264 at YMH) samples was collected from 296 subjects (161 at CGMH and 135 at YMH). During the two survey periods within the duration of 6 months, 104 subjects and 129 subjects at CGMH and YMH respectively participated in both surveys; 12 subjects at CGMH in first survey, 45 subjects at CGMH in second survey, and 6 subjects at YMH in second survey participated in one.

The prevalence of MSSA and MRSA in the first time and second time was shown in Table 1-1. The overall prevalence of MRSA colonization was 4.2% at CGMH and 3.4% at YMH. No significant difference in the percentages of nasal MSSA and MRSA carriage rate between two hospitals. Table 1-2 showed the results from patients participating in both samplings. The population received sampling twice had no difference in carriage rate between general population in our research.

The comparison of demographic and clinical features between MRSA and non-MRSA colonization among all the 296 subjects are shown in Table 2. No significant association ($P > 0.05$) with MRSA colonization detected for sex

distribution, age distribution, duration of dialysis, underlying disease, blood access, and other risk factors, neither was MSSA colonization.

Due to the lack of clinical records of antimicrobial susceptibility of previous *S. aureus* clinical culture and current antibiotics use at YMH, those data only at CGMH was shown in Table 3. No significant difference was observed for previous MSSA or MRSA infection in 1 year, and antibiotics use in 1 month before sampling.

Twenty MRSA isolates were identified from 19 subjects. Table 4 shows the molecular characteristics of all 20 isolates. Five PFGE patterns were identified. PFGE patterns D with *spa* gene type 437 (accounting for 45% of the colonized isolates) and C with *spa* gene type 437 (accounting for 25% of the colonized isolates) were the 2 most common patterns. Of 20 isolates, 7 (35%) were SCC*mec* type IV, 9 (45%) were SCC*mec* type V_T, and 4 (20 %) could not be determined for SCC*mec* type. Eight of the 9 isolates of PFGE type D carried PVL genes, whereas only 1 of 8 isolates classified as PFGE type C and none of other isolates harbored PVL genes. Three quarters of all isolates belonged to endemic community-associated (CA) clones in Taiwan as sequence type (ST) 59 and ST338.

All the MRSA strains were resistant to penicillin and susceptible to linezoid, teicoplanin, and vancomycin. Overall antibiotics to erythormycin, doxycyclin, clindamycin, trimethoprim- sulfamethoxazole (TMP-SMX), and fusidic acid were detected in 30%, 95%, 40%, 95%, and 90% of the isolates susceptibility at two hospitals, respectively. No significant difference was observed in susceptibility between two hospitals. (Table 5.)

During this study period, nasal and skin decolonization was done twice. After the first decolonization, 8 of 9 MRSA carriers were decolonized successfully. The second time, 11 MRSA carriers were all decolonized. The subject without successful decolonization in the first decolonization still had MRSA colonization in the second survey, and two isolates from the first and second samplings belonged to one indistinguishable clone characterized as ST338/PFGE D/SCC*mec* V_T/PVL-positive. The follow-up sampling after the first decolonization showed that the isolate had the same PFGE type with the previous isolate, but no further molecular analysis was done for this isolate.

Due to the lack of well clinical monitoring at YMH, infection events were only detected at CGMH. Two patients (1.24%) in the medical center, one with MRSA colonization (9.1%), developed MRSA infection. Unfortunately, both clinical isolates could not be obtained from CGHM. No molecular compare between clinical isolates and isolates from precious colonization was observed.

Discussion

Results from this study showed that the mean MRSA carriage rate of hemodialysis patients was 3.8%. This MRSA carriage rate was similar to that of patients visiting emergency room at CGMH[29] and adults for health examination in Taiwan[30]. The author thought most of hemodialysis outpatients came from community settings. Due to both out-patient hemodialysis clinics were located on independent spaces at both hospitals, there was no frequent exposure to at-risk (of MRSA infection or colonization) patients such as patients form intensive care unit (ICU).

Compared to previous studies in Taiwan, mean MRSA carriage rate among hemodialysis patients was relatively lower than that in northern Taiwan (9.48%)[31], but was more comparable to a study (2.36%) in southern Taiwan[32].

No significant difference in carriage rate was found between patients treated at the medical center and the local hospital in this study. In the other words, the results at two hospitals were comparable in terms of MSSA and MRSA carriage rate, antibiotics susceptibility of isolates, and molecular characteristics of strains. The researchers thought the out-patient hemodialysis environments at a local hospital and a medical center were similar.

Previous studies regarding the risk factors of *S.aureus* nasal colonization indicated that hemodialysis was associated an increased risk of MSSA or MRSA colonization[29, 33, 34]. In this study, no additional significant risk factor for MRSA or MSSA nasal colonization was identified among patients receiving maintenance hemodialysis.

This research showed that MRSA isolates of hemodialysis patients presented several characteristics of community-associated strains, while the traits of CA-MRSA, such as belonging to PFGE C or D, being of SCC*mec* IV or V_T[35], and carrying the PVL gene[15]. Most isolates shared common molecular characteristics and >60% of the isolates belonged to one of two major clones characterized by ST59 (or its variant ST338) / PFGE D / SCC*mec* V_T / PVL positive/ *spa* type 437 and ST59 / PFGE C / SCC*mec* IV / PVL negative/ *spa* type 437. Both were dominant community strains in

Taiwan, which had been discussed previously [14]. This situation of community strains being transmitted to healthcare facilities was indicated. The patient with strains belonged to ST30 had travel history to other Asian countries. The isolation of ST45 was first reported in 2011 in Taiwan[36]. Since the ST45 isolate in this research was un-typeable for SCC*mec*, novel typing method was needed. Other emerging CA clones, such as PFGE type U, ST8 and ST573 needed further investigation. According to previous study, CA-MRSA isolates were more susceptible to TMP-SMX than HA-MRSA which was the only drug associated with difference between two strains[37]. It was also parallel to molecular characteristics in this research.

As presented in the former portion, a higher proportion was found of hemodialysis patients with MRSA colonization (9.1%) who developed a MRSA infection than that without MRSA colonization (0.6%). Although decolonization for MRSA carriers was done successfully, the infection event of this group was still noted. Since no clinical isolate was obtained, the researches could not provide the direct evidence of association between MRSA colonization and subsequent infection.

MRSA decolonization referred to the use of nasal mupirocin ointment and chlorhexidine bodywash to eradicate nasal and skin colonization[19]. In present study, decolonization for one MRSA carrier with ST338 colonized was failed after the first intervention. Chlorhexidine susceptibility of MRSA clones had been studied previously[22]. Isolates belonged to ST338 was included and shown to have low to borderline chlorhexidine resistance. Due successful decolonization in second time, drug compliance of this patient

was the other possibility of decolonization failed. Overall, decolonization for all strains from patients receiving hemodialysis was effective which indicated the development of resistance was not elicited. The issue whether decolonization of MRSA decreased subsequent infection in this group needed further observation.

Among patients participated in whole study period, MSSA colonization in nasal had ever been found in 11 patients (10.6%) in CGMH and 15 patients (11.9%) in YMH, whereas 18 patients (69.2%, 9 at each hospital) had MSSA nasal colonization in both sampling. Only one patient with different MSSA strain was confirmed using PFGE typing. Another 17 patients (65.4%) are persistently colonized with identical strain in both surveys. Correlating with the decolonization of MRSA in this study, mupirocin nasal ointment and chlorhexidine bodywash play an important role in eradicating carriage of *S. aureus*.

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Table 1-1.

Comparison the prevalence of methicillin-resistant *S. aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA) between two Hospitals among all patients

Colonization	No. (%) of subjects			Odds ratio	*p* value[a]
	CGMH	YMH	Total	(95% CI)	
Subject No. of 1st sampling	**116**	**129**	**245**		
MSSA	14 (12.1)	16 (12.4)	30 (12.2)	0.969(0.451~2.084)	0.937
MRSA	6 (5.2)	3 (2.3)	9 (3.7)	2.291(0.560~9.377)	0.314
Subject No. of 2nd sampling	**149**	**135**	**284**		
MSSA	17 (11.4)	17 (12.6)	34 (12.0)	0.894(0.437~1.830)	0.759
MRSA	5 (3.4)	6 (4.4)	11 (3.9)	0.747(0.223~2.504)	0.635
Total No. of samples	**265**	**264**	**529**		
MSSA	31(11.7)	33(12.5)	64(12.1)	0.927(0.550~1.564)	0.777
MRSA	11(4.2)	9(3.4)	20(3.8)	1.227(0.500~3.012)	0.655

Table 1-2.

Results from patients participated in both samplings

Colonization	No. (%) of subjects	Odds ratio	*p* value[a]

		CGMH (n=104)	YMH (n=129)	Total (n=233)	(95% CI)	
1st sampling	**MSSA**	12(11.5)	16(12.4)	28(12.0)	0.921(0.415~2.045)	0.840
	MRSA	6(5.8)	3(2.3)	9(3.9)	2.571(0.627~10.541)	0.193
2nd sampling	**MSSA**	10(9.6)	17(13.2)	27(11.6)	0.701(0.306~1.604)	0.398
	MRSA	3(2.9)	5(3.9)	8(3.4)	0.737(0.172~3.157)	0.735

CGMH: Chang Gung Memorial Hospital, YMH: Yang Ming Hospital, CI: confidence interval

[a] Fisher's exact test was used for extreme proportions (expected count <5) instead of Pearson's chi-square test

Table2.

Demographics and clinical characteristics of hemodialysis patients with and without methicillin-resistant *S. aureus* (MRSA) colonization.

Patient characteristics and clinical data	No. (%) of subjects			Odds ratio	95% confidence interval	*p* value[a]
	Total (n=296)	MRSA (n=19)	Non-MRSA (n=277)			
Male	136(45.9)	6(31.6)	130(46.9)	0.522	0.193~1.413	0.194
Age						
19-29	6(2.0)	0	6(2.1)	0.934	0.906~0.963	1.000
30-59	155(52.4)	10(52.6)	145(52.3)	1.011	0.399~2.566	0.981
>=60	135(45.6)	9(47.4)	126(45.5)	1.079	0.425~2.737	0.873
Underlying diseases						
DM	125(42.2)	11(57.9)	114(41.2)	1.966	0.767~5.041	0.153
Hypertension	194(65.5)	16(84.2)	178(64.3)	2.920	0.830~10.268	0.081
HBV carrier	32(10.8)	0	32(11.6)	0.928	0.897~0.960	0.241
HCV carrier	46(15.5)	2(10.5)	44(15.9)	0.620	0.138~2.781	0.406
Liver cirrhosis	8(2.7)	0	8(2.3)	0.934	0.905~0.963	1.000
Gastric ulcer	92(31.1)	5(26.3)	87(31.4)	0.780	0.272~2.234	0.643

History of GI bleeding	26(8.8)	3(15.8)	23(8.3)	2.071	0.562~7.635	0.226
Asthma	2(0.7)	0	2(0.7)	0.935	0.908~0.964	1.000
History of TB infection	5(1.7)	0	5(1.8)	0.935	0.907~0.964	1.000
COPD	16(5.4)	0	16(5.8)	0.932	0.903~0.962	0.610
Cancer	25(8.4)	1(5.3)	24(8.7)	0.586	0.075~4.580	1.000
Current disease						
Pneumonia	3(1.0)	0	3(1.1)	0.935	0.907~0.964	1.000
URTI	51(17.2)	4(21.1)	47(17.0)	1.305	0.415~4.108	0.752
Other risk factors						
Hospitalization [c]	95(32.1)	4(21.1)	91(35.0)	0.545	0.176~1.689	0.287
Previous *S. aureus* inf. [c,d]	42(14.2)	4(21.1)	38(13.7)	1.677	0.529~5.323	0.325
Skin inf. of *S. aureus* [c,d,e]	13(4.4)	1(5.3)	12(4.3)	1.227	0.151~9.970	0.586
Previous catheter related inf [c].	34(11.5)	3(15.8)	31(11.2)	1.488	0.410~5.397	0.467
Using of immunosuppressant	18(6.1)	2(10.5)	16(5.8)	1.919	0.407~9.039	0.324
Alcohol drinking	24(8.1)	0	24(8.7)	0.930	0.900~0.961	0.381
Average duration of HD(year)[b]	7.03±0.35	5.60±1.28	7.13±0.36			0.289
Duration > 3 years	11(57.9)	195(70.4)	206(69.6)	0.578	0.224~1.490	0.252
Duration > 5 years	8(42.1)	152(54.9)	160(54.1)	0.598	0.233~1.533	0.280

Blood access						
Hickman	22(7.4)	1(5.3)	21(7.6)	0.677	0.086~5.326	1.000
A-V fistula	180(60.8)	11(57.9)	169(61.0)	0.879	0.342~2.254	0.788
Gortex	94(31.8)	7(36.8)	87(31.4)	1.274	0.485~3.347	0.623
Other catheter [f]	8(2.7)	2(10.5)	6(2.2)	5.314	0.997~28.331	0.087

DM: diabetes mellitus, HBV: hepatitis B virus , HCV: hepatitis C virus, GI: gastrointestinal, TB: tuberculosis, COPD: chronic obstructive pulmonary disease, URTI: upper respiratory tract infection, inf.: infection, HD: hemodialysis, A-V: arterial venous

[a] For categorical variables, Fisher's exact test was used for extreme proportions (expected count <5) instead of Pearson's chi-square test

[b] data was presented as the mean value ± standard error of the mean for continuous variables. Performed by Student *t* test

[c] any event happened in one year before sampling.

[d] including general *S. aureus* infection without known susceptibility or resistance of antibiotics

[e] including impetigo, furuncle, carbuncle, cellulitis, and abscess

[f] Including Foley and tracheostomy tube

Table 3.

Association of methicillin-resistant *S. aureus* (MRSA) colonization with clinical data only obtained at Chang Gung Memorial Hospital

Clinical data	No. (%) of subjects		Odds ratio	95% confidence interval	*p* value[a]
	MRSA (n=11)	Non-MRSA (n=150)			
Previous MRSA infection in 1 year	1 (9.1)	2 (1.3)	7.400	0.617~88.756	0.192
Previous MSSA infection in 1 year	0	4 (2.7)	0.930	0.891~0.971	1.000
Antibiotics use in last 1 month[b]	2(18.2)	40(26.7)	0.611	0.127~2.950	0.730
Last admission(year)[c]	3.01±0.86	2.81±0.26			0.838

MRSA: methicillin-resistant *S. aureus*, MSSA: methicillin-susceptible *S. aureus*

[a] Fisher's exact test was used for extreme proportions (expected count <5) instead of Pearson's chi-square test

[b] Any category of antibiotics as oral intake or intravenous administration

[c] Indicated years after last admission. Data was presented as the mean value ± standard error of the mean for continuous variables. Performed by Student *t* test

Table 4.

Distribution of PFGE patterns and other molecular analysis of all 20 methicillin-resistant *S. aureu* isolates

PFGE pattern	**No. (%) of isolates (n=20)**	**SCC*mec* type**	**Presence of PVL genes**	**MLST type**	***spa* gene type**
C	5(25)	IV	1	59	t0437
D	9(45)	V_T	8	59,338	t0437
AG	1(5)	IV	0	30	t019
BR	1(5)	IV	0	8	t008
BM	3(15)	UT	0	45	t1081
U	1(5)	UT	0	573	t3525

PFGE: pulsed-field gel electrophoresis, SCC*mec* staphylococcal chromosomal cassette *mec*, MLST: multilocus sequence type, PVL: Panton-Valentine leukocidin, UT: untypeable

Table 5. Antimicrobial susceptibility of 20 MRSA isolates, stratified by patient from Chang-Gung Memorial Hospital(CGMH) or Yang Ming Hospital(YMH)

Antibiotics	Total (n=20)	CGMH (n=11)	YMH (n=9)	*p* value[a]
Erythormycin	6 (30%)	3 (27%)	3 (33%)	0.769
Doxycyclin	19 (95%)	10 (91%)	9 (100%)	0.353
Clindamycin	8 (40%)	4 (36%)	4 (44%)	0.714
TMP-SMX	19 (95%)	10 (91%)	9 (100%)	0.353
Penicillin	0	0	0	
Oxicillin	0	0	0	
Linezoid	20 (100%)	11 (100%)	9 (100%)	
Fusidic acid	18 (90%)	11 (100%)	7 (78%)	0.099
Teicoplanin	20 (100%)	11 (100%)	9 (100%)	
Vancomycin	20(100%)	11 (100%)	9 (100%)	

TMP-SMX: trimethoprim-sulfamethoxazole

[a] Fisher's exact test was used for extreme proportions (expected count <5) instead of Pearson's chi-square test