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Methicillin-Resistant *Staphylococcus aureus* Ocular Infection in Taiwan

Clinical Features, Genotying, and Antibiotic Susceptibility

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Abstract: Methicillin-resistant *Staphylococcus aureus* (MRSA) infection is an important public health issue. This observational study aimed to characterize clinical features, antibiotic susceptibility, and genotypes of ocular infections caused by MRSA based on the clinical and molecular definitions of community-associated (CA) and healthcare-associated (HA) strains.

Fifty-nine patients with culture-proven *S aureus* ocular infection were enrolled from January 1, 2010 to December 31, 2011 at Chang Gung Memorial Hospital, Taiwan. Antibiotic susceptibility was verified using disk diffusion/E test. For characterization, staphylococcal cassette chromosome *mec* (SCC*mec*), pulsed-field gel electrophoresis (PFGE), multilocus sequence type (MLST), and Panton–Valentine leukocidin (PVL) gene, were performed. MRSA isolates from the patients with HA factors were classified as clinically defined HA-MRSA, and those carrying SCC*mec* type I to III as molecularly defined HA-MRSA.

Thirty-four patients with MRSA ocular infection were identified. The most common clone of CA-MRSA and HA-MRSA isolates was ST59/PFGE type D/SCC*mec* IV,V_T/PVL (+) (n = 12) and CC 239/PFGE type A/SCC*mec* III, III_A/PVL(−) (n = 10), respectively. All the 11 patients with molecularly defined HA-MRSA infections and 50% of the 22 patients with molecularly defined CA-MRSA infections were found to have HA factors ($P = .005$). CA-MRSA tended to cause lid infections, whereas HA-MRSA tended to cause corneal infections. Contrary to HA-MRSA isolates, nearly all the CA-MRSA isolates were susceptible to trimethoprim/sulfamethoxazole and fluoroquinolones under either clinical or molecular classifications.

In Taiwan, CA-MRSA isolates exhibited considerably higher susceptibility to fluoroquinolones when compared with HA-MRSA isolates. A strong correlation was observed between the HA factors and molecularly defined HA-MRSA isolates.

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Abbreviations: CA = community-associated, HA = healthcare-associated, MLST = multilocus sequence type, MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-sensitive *Staphylococcus aureus*, PFGE = pulsed-field gel electrophoresis, PVL = Panton–Valentine leukocidin, SCC*mec* = staphylococcal cassette chromosome *mec*, Spa = *S. aureus* protein A, TMP/SMX = trimethoprim/sulfamethoxazole.

INTRODUCTION

Staphylococcus aureus has been a common pathogen that causes infectious diseases at various sites in the human body. Since the identification of methicillin-resistant *S aureus* (MRSA) in 1960s, it has been a crucial concern in several infectious diseases and was initially associated with hospital-acquired pathogens. However, its prevalence has increased in healthy people without risk factors for exposure to healthcare facilities.[1,2] Thereafter, MRSA strains were arbitrarily classified into 2 groups, namely community-associated (CA) and healthcare-associated (HA)-MRSA. Compared with HA-MRSA isolates, CA-MRSA isolates had different molecular characteristics in addition to clinical features.[3,4] With regard to the antibiotic susceptibility of *S aureus*, a mobile genetic element, staphylococcal cassette chromosome *mec* (SCC*mec*), plays an essential role and is a major molecular hallmark for MRSA classification. MRSA strains with type I to III SCC*mec* elements, which are responsible for resistance to numerous classes of antibiotics, were associated with HA-MRSA,[5] whereas those carrying type IV and V (V_T) SCC*mec* elements were commonly identified in CA-MRSA strains.[6] In addition, the gene coding for Panton–Valentine leukocidin (PVL), a cytotoxin that causes leukocyte destruction, is associated with increased virulence of *S aureus* and is frequently present in CA-MRSA strains.[7] Moreover, the primary clinical manifestations of CA-MRSA strains are skin and soft tissue infections.[8] Nevertheless, the distinction between CA- and HA-MRSA becomes blurred, whereas CA-MRSA strains are transmitting to hospital settings.[9]

Until recently, limited studies focused on the issue of MRSA ocular infections stratified by CA- and HA-MRSA strains.[10–16] Most studies regarding CA- and HA-MRSA ocular infections, including our previous study, were based on the clinical definitions without molecular characteristics,[10–13,16]

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whereas some with molecular characteristics did not report the specific clinical manifestations.[14,15] Meanwhile, the recent increased antibiotic resistance in MRSA ocular infections has become a critical concern.[17,18] Hence, we conducted a study to evaluate the clinical features, molecular characterization, and antibiograms of MRSA ocular infections and compare CA- and HA-MRSA isolates based on both clinical and molecular definitions, and to seek for the clinical application of these results.

MATERIALS AND METHODS

Ethics Statement

This study followed the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board (IRB) of Chang Gung Memorial Hospital (CGMH), Taiwan (IRB102–2184C). All data were deidentified and anonymously reviewed to protect the privacy of the study participants; therefore, the need for informed consent was waived by the IRB.

Study Population and Data Collection

From January 1, 2010 to December 31, 2011, *S aureus* isolates from the patients with ocular infections were prospectively collected in the microbiology laboratory of CGMH, a 3700-bed medical center in Northern Taiwan. In total, 59 patients with *S aureus* ocular infections were identified. Medical records of these cases were retrospectively reviewed and collected.

The clinical data, including demographics, underlying disease, ocular history, recent medication history (immunosuppressants and antibiotics), HA factors (described later), primary diagnosis, management, and outcomes, were collected based on the electronic charts of the patients. The recorded underlying diseases included diabetes mellitus, hypertension, pulmonary disease, renal disease, liver disease, malignancy, and current nonocular infections. The ocular history included the use of contact lenses, ocular trauma, ocular surface disease, and ocular surgery. According to the ocular structure involved, the infections were classified in 7 categories based on diagnoses: lid disorder, lacrimal system disorder, conjunctivitis, keratitis, endophthalmitis, wound infection, and others. When a patient was diagnosed with >1 ocular infection, the primary pathology or the most severe diagnosis was considered.

Drug Susceptibility Tests

The antimicrobial susceptibility of all *S. aureus* isolates to antibiotics, including cefoxitin, penicillin, clindamycin, erythromycin, trimethoprim/sulfamethoxazole (TMP-SMX), teicoplanin, and vancomycin, was routinely performed using the disk diffusion method in our microbiology laboratory according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI) antimicrobial susceptibility testing standards. We used cefoxitin instead of oxacillin/methicillin to test for β-lactam antibiotic resistance. In addition, we used an E-test (BioMerieux SA, Marcy-I'Etoile, France) to determine the susceptibility to fluoroquinolones including ciprofloxacin, levofloxacin, gatifloxacin, and moxifloxacin, that were not included in the antibiotic susceptibility profiles for *S aureus* in our microbiology laboratory.

Molecular Typing and Detection of *PVL* Gene

The molecular methods used in this study included pulsed-field gel electrophoresis (PFGE) with *Sma*I digestion, SCC*mec* typing,[19] multilocus sequence type (MLST),[20] and *S. aureus* protein A (*spa*) gene typing.[21] In addition, the presence of PVL genes[22] was examined. The details of the procedures have been described previously.[19–23] All the MRSA isolates were molecularly characterized based on PFGE, PVL, and SCC*mec*. The PFGE genotypes were designated in alphabetical order, as in our previous studies; any new type, when identified, was designated consecutively. PFGE patterns with <4-band differences from an existing genotype were defined as subtypes. MLST and *spa* gene typing were examined for selective isolates of representative PFGE patterns.

CATEGORIZATION

Patients with MRSA infection were classified into 2 groups, CA- and HA-MRSA, based on the molecular and clinical criteria. The molecular criteria were derived from previous MRSA studies conducted in Taiwan[6]; isolates carrying type I to III SCC*mec* were defined as molecular HA-MRSA, whereas those carrying type IV or V SCC*mec* were defined as molecular CA-MRSA. An isolate without a typable SCC*mec* was excluded for further analysis. The clinical HA criteria were based on the definition proposed by the Centers for Disease Control and Prevention Active Bacterial Core Surveillance sites,[24] including specimens obtained after 48 hours of admission, history of hospitalization, surgery, dialysis, or living in a long-term-care facility within 1 year, any permanent indwelling catheter, and any report of prior positive culture for MRSA.

Statistical Analysis

In descriptive statistics, the variables of interest were either presented as mean ± standard deviation or a number with a percentage. The intergroup differences in the variables were compared using *t*, Pearson χ^2, or Fisher exact tests. A 2-tailed *P* value <0.05 was considered statistically significant. All the data analyses were performed using SPSS Version 19.0 (IBM, Armonk, NY).

RESULTS

Among the *S aureus* strains isolated from the 59 study patients, 25 (42.4%) were methicillin-sensitive *S aureus* (MSSA) and 34 (57.6%) were MRSA.

Comparison of Clinical Features and Drug Susceptibility Between MRSA and MSSA

Supplementary Table 1, http://links.lww.com/MD/A452 presents comparisons of clinical features between the MSSA and the MRSA groups. No significant differences were observed in sex composition, mean age, underlying disease, ocular history, diagnosis, outcome, and patients with HA factors between both groups. In both groups, keratitis was the most common ocular diagnosis, followed by conjunctivitis.

Supplementary Table 2, http://links.lww.com/MD/A452 lists comparisons of antibiotic susceptibility between the MSSA and the MRSA groups. The MRSA strains exhibited greater resistance to several antibiotics, including clindamycin, erythromycin, TMP-SMX, and 4 fluoroquinolones than did the MSSA strains, whereas both MRSA and MSSA strains were susceptible to teicoplanin and vancomycin.

Molecular Typing of MRSA

Table 1 summarizes the molecular typing of the 34 MRSA isolates. All but 3 isolates clustered in 3 PFGE patterns, namely types A, C, and D. PVL genes were only detected in the isolates

TABLE 1. Molecular Characteristics of 34 Clinical Methicillin-Resistant *S aueus* Isolates From Patients With Ocular Infections, Stratified by Pulsed-Field Gel Electrophoresis

PFGE	No. (%) of Isolates	Community-associated*	Healthcare-associated*	SCC*mec* Type	Presence of *PVL* Genes	MLST Type†	*Spa* Gene Type†
A	10 (29.4)	0	10	III, III_A	0	239, 89	t037, t275, t375
C	9 (26.5)	3	6	IV	0	59, 2952‡	t437
D	12 (35.3)	8	4	IV,V_T	12	59	t437, t441, t4145
F	1 (2.9)	0	1	II	0	5	t002
BM	1 (2.9)	1	0	Untypable	0	45	t1081
W	1 (2.9)	0	1	IV	0	1	t2457

MLST = multilocus sequence type, PFGE = pulsed-field gel electrophoresis, PVL = Panton-Valentine leukocidin, SCC*mec* = staphylococcal cassette chromosome *mec*, *Spa*, *S* = *S. aureus* protein A.
* Based on clinical definition.
† MLST/*Spa* gene was performed in selected isolates.
‡ ST2952 is a single-locus variant of ST59.

TABLE 2. Comparison of Clinical Features Between HA-MRSA and CA-MRSA Based on Clinical Definition*

	No. (%) of Subjects		
	CA-MRSA (n = 12)	HA-MRSA (n = 22)	*P*†
General information			
Male	6 (50.0)	11 (50.0)	1
Age‡	48.3 ± 21.9	52.0 ± 28.8	0.707
Underlying disease			
Diabetes mellitus	3 (25.0)	9 (40.9)	0.465
Hypertension	4 (33.3)	7 (31.8)	1
Pulmonary disease	2 (16.7)	2 (9.1)	0.602
Renal disease	1 (8.3)	5 (22.7)	0.389
Liver disease	1 (8.3)	1 (4.5)	1
Malignancy	0	3 (13.6)	0.537
Current infection§	0	8 (36.4)	0.030
Recent antibiotic use	0	8 (36.4)	0.030
Ocular history			
Contact lens	1 (8.3)	0	0.353
Ocular trauma	0	4 (18.2)	0.273
Ocular surface disease	5 (41.7)	9 (40.9)	1
Surgery history	2 (16.7)	15 (68.2)	0.004
Diagnosis			
Lid disorder	6 (50.0)	0	0.001
Conjunctivitis	3 (25.0)	4 (18.2)	0.677
Keratitis	3 (25.0)	15 (68.2)	0.016
Endophthalmitis	0	0	1
Wound infection	0	3 (13.6)	0.537
Treatment and outcome			
Surgical intervention	2 (16.7)	4 (18.2)	1
Outpatient treatment, cured	10 (83.3)	5 (22.7)	0.001
Hospitalization, cured	2 (16.7)	13 (59.1)	0.017

CA-MRSA = community-associated methicillin-resistant *S aureus*, HA-MRSA = healthcare-associated methicillin-resistant *S aureus*.
* Clinical definition: HA-MRSA included specimens (MRSA culture) after 48 hours of admission; history of hospitalization, long-term care facility within 1 year, under dialysis; living in healthcare facility; permanent indwelling catheter; a known positive culture for MRSA before; history of surgery in 1 year.
† Fisher exact test instead of Pearson χ^2 test was performed when any expected count was <5 by statistical analysis.
‡ Independent-samples *t* test was used.
§ Infection other than ocular infection.

of PFGE type D. The most predominant clone was PFGE type D/SCC*mec* IV,V_T/Sequence type (ST) 59/*spa* clonal complex (CC) t437 (12 isolates, 35.3%), which is considered as a common endemic CA clone in Taiwan, followed by PFGE A/SCC*mec* III, III_A/CC 239/*spa* CC t037 (10 isolates, 29.4%), which is considered an endemic HA clone in Taiwan. In addition, the isolates with PFGE C/SCC*mec* IV/CC 59/*spa* t437, which are the other one common endemic CA clone, were identified in 9 patients (26.5%).

Comparison of Clinical Features and Drug Susceptibility Between CA- and HA-MRSA Based on Clinical Definition

Based on the clinical definition, 12 isolates were classified as CA-MRSA (35.3%) and 22 as HA-MRSA (64.7%). Table 2 illustrates the comparisons between clinically defined CA- and HA-MRSA. No significant differences were observed in terms of demographics and underlying systemic diseases except for current infections ($P = .030$) between the 2 groups. The rate of recent antibiotic use in the HA-MRSA group was significantly higher than that in the CA-MRSA group ($P = .030$). Patients with HA-MRSA infection exhibited a higher rate (68.2% vs 16.7%) of ocular surgery history ($P = .004$). No patient with HA-MRSA infection presented as lid disorder, which were caused predominantly by CA-MRSA strains (50% of CA isolates, $P = .001$). In contrast, the rate of keratitis caused by HA-MRSA strains was higher than that caused by CA-MRSA strains (68.2% vs 25%, $P = .016$). Patients with CA-MRSA infection were primarily managed at outpatient clinics (83.3% of CA-MRSA isolates, $P = .001$), whereas those with HA-MRSA infections were more hospitalized (59.1% of HA isolates, $P = .017$).

Left portion of Table 3 lists the drug susceptibility of MRSA strains based on clinical definition. All MRSA isolates were susceptible to vancomycin and teicoplanin, but both CA- and HA-MRSA were resistant to erythromycin and clindamycin. All CA-MRSA strains were susceptible to TMP-SMX, whereas the HA-MRSA strains exhibited lower susceptibility to TMP-SMX (63.6%, $P = .03$). In addition, the CA-MRSA strains were more susceptible to fluoroquinolones (87.5%-100%) than were the HA-MRSA strains (50.0%–63.6%, $P = 0.024–0.053$).

Comparison of Clinical Features and Drug Susceptibility Between CA- and HA-MRSA Based on Molecular Definition

Excluding 1 isolate with untypable SCC*mec*, 22 isolates were classified as CA-MRSA strains (66.7%) and 11 as HA-MRSA strains (33.3%) based on molecular definition.

Table 4 summarizes comparisons of clinical features between the patients with molecularly defined CA- and HA-MRSA infections. There were only 2 significant differences found between 2 groups: ocular trauma history ($P = 0.008$) and HA factors ($P = 0.005$). All patients with a history of ocular trauma developed HA-MRSA infections. HA factors were identified in all patients with molecularly defined HA-MRSA infections and 50% (11/22) of the patients with molecularly defined CA-MRSA infections.

Right portion of Table 3 lists the drug susceptibility of molecularly defined CA-MRSA and HA-MRSA isolates, which was similar to that of clinically defined CA- and HA-MRSA isolates, but the differences were more statistically significant. One molecularly defined CA-MRSA isolate was resistant to ciprofloxacin but susceptible to the other 3 fluoroquinolones and TMP-SMX; all the other molecularly defined CA-MRSA strains were susceptible to TMP-SMX and fluoroquinolones. Conversely, the molecularly defined HA-MRSA strains exhibited lower susceptibility to TMP-SMX and fluoroquinolones (27.3% and 9.1%–27.3%, respectively, all $P < 0.001$).

TABLE 3. Antibiotic Susceptibility Tests* of HA-MRSA and CA-MRSA Isolates for Ocular Infections

	No. (%) of Subjects					
	Clinical Definition†			Molecular Definition†		
Antibiotics	CA-MRSA (n = 12)	HA-MRSA (n = 22)	P‡	CA-MRSA (n = 22)	HA-MRSA (n = 11)	P‡
Clindamycin	2 (16.7)	0	0.118	2 (9.1)	0 (0)	0.542
Erythromycin	2 (16.7)	0	0.118	2 (9.1)	0 (0)	0.542
Cefoxitin	0	0	1	0 (0)	0 (0)	1
Penicillin	0	0	1	0 (0)	0 (0)	1
TMP-SMX	12 (100)	14 (63.6)	0.030	22 (100)	3 (27.3)	<0.001
Teicoplanin	12 (100)	22 (100)	1	22 (100)	11 (100)	1
Vancomycin	12 (100)	22 (100)	1	22 (100)	11 (100)	1
Ciprofloxacin	11 (91.7)	11 (50.0)	0.024	21 (95.5)	1 (9.1)	<0.001
Levofloxacin	11 (87.5)	12 (54.5)	0.053	22 (100)	1 (9.1)	<0.001
Gatifloxacin	12 (100)	13 (59.1)	0.013	22 (100)	2 (18.2)	<0.001
Moxifloxacin	12 (100)	14 (63.6)	0.030	22 (100)	3 (27.3)	<0.001

CA-MRSA = community-associated methicillin-resistant *S. aureus*, HA-MRSA = healthcare-associated methicillin-resistant *S. aureus*, TMP-SMX = Trimethoprim/Sulfamethoxazole.

* Intermediate interpreted as resistant; the susceptibility to fluoroquinolones was tested by E test, and others were tested by disk diffusion method.

† Clinical definition: please see the text or footnotes of Table 2. Molecular definition: CA-MRSA included SCC*mec* type IV & V and HA-MRSA included SCC*mec* type I-III, the strain with untypable SCC*mec* was excluded.

‡ Fisher exact test instead of Pearson χ^2 test was performed when any expected count was <5 by statistical analysis.

TABLE 4. Comparison of Clinical Characteristics Between HA-MRSA and CA-MRSA Based on Molecular Definition*

	No. (%) of Subjects		
	CA-MRSA (n = 22)	**HA-MRSA (n = 11)**	***P*†**
General information			
Male	10 (45.5)	7 (63.6)	0.325
Age‡	52.9 ± 24.7	47.5 ± 31.0	0.590
Underlying disease			
Diabetes mellitus	6 (27.3)	5 (45.5)	0.437
Hypertension	8 (36.4)	3 (27.3)	0.709
Pulmonary disease	2 (9.1)	2 (18.2)	0.586
Renal disease	3 (13.6)	3 (27.3)	0.375
Liver disease	2 (9.1)	0	0.542
Malignancy	1 (4.5)	2 (18.2)	0.252
Current infection§	4 (18.2)	4 (36.4)	0.391
Recent antibiotic use	4 (18.2)	4 (36.4)	0.391
Ocular history			
Contact lens	1 (4.5)	0	1
Ocular trauma	0	4 (36.4)	0.008
Ocular surface disease	10 (45.5)	3 (27.3)	0.456
Surgery history	10 (45.5)	6 (54.5)	0.622
HA factors#	11 (50.0)	11 (100)	0.005
Diagnosis			
Lid disorder	6 (27.3)	0	0.077
Conjunctivitis	4 (18.2)	3 (27.3)	0.611
Keratitis	9 (40.9)	8 (72.7)	0.085
Endophthalmitis	0	0	1
Wound infection	3 (13.6)	0	0.534
Treatment and outcome			
Surgical intervention	3 (13.6)	3 (27.3)	0.375
Outpatient treatment, cured	12 (54.5)	2 (18.2)	0.067
Hospitalization, cured	8 (36.4)	7 (63.6)	0.138

CA-MRSA = community-associated methicillin-resistant *S. aureus*, HA = healthcare-associated, HA-MRSA = healthcare-associated methicillin-resistant *S. aureus.*

* Molecular definition: CA-MRSA included SCC*mec* type IV & V and HA-MRSA included SCC*mec* type I–III, the strain with untypable SCC*mec* was excluded.

† Fisher exact test instead of Pearson χ^2 test was performed when any expected count was <5 by statistical analysis. *P* value <0.05 was significant.

‡ Independent-samples *t* test was used.

§ Infection other than ocular infection.

HA factors included specimens (MRSA culture) after 48 hours of admission; history of hospitalization, long-term care facility within one year, under dialysis; living in healthcare facility; permanent indwelling catheter; a known positive culture for MRSA before; history of surgery in 1 year.

Validity of the Predictors for Molecularly Defined HA-MRSA

Considering the significant differences in the drug susceptibility to TMP-SMX between CA- and HA-MRSA, we tried to evaluate whether molecularly-defined HA strains could be predicted by the presence of HA factors and/or TMP-SMX resistance. Table 5 represents the results of validity analysis. As taken molecularly defined HA-MRSA as a gold standard, the sensitivity, specificity, positive predictive value, and negative predictive value of the presence of any HA factor were 100%, 50%, 50%, and 100%, respectively, and those of TMP-SMX resistance were 72.7%, 100%, 100%, and 88%, respectively.

DISCUSSION

This study extended our previous 10-year study,[12] which specifically compared ocular CA- and HA-MRSA isolates in Taiwan, and replenished its insufficiency of genotyping, and antibiograms regarding fluoroquinolones. Our findings demonstrated that HA factors could distinguish patients with molecularly defined HA-MRSA ocular infections from those with molecularly defined CA-MRSA infections. In addition, TMP-SMX and fluoroquinolones revealed a considerably higher degree of activity against the CA-MRSA isolates than HA-MRSA isolates, regardless of the clinical or molecular definition.

Our study showed that the distribution of molecular characteristics for both CA- and HA-MRSA isolates was consistent with those reported from nonocular infections in Taiwan,[25] which revealed CC59 with SCC*mec* IV/V_T and CC239 with SCC*mec* III/III_A were predominant in CA and HA clones, respectively. ST2952, a single locus variant of ST59, identified in this study was reported for the first time. In this study, ST45 with untypable SCC*mec* was not categorized into a molecular CA or HA group based on our definition, although this clone

TABLE 5. Prediction of Molecularly Defined HA-MRSA by Healthcare-Associated Factors and TMP-SMX Resistance

	Molecularly Defined HA-MRSA					
Predictors	**Yes (n = 11)**	**No (n = 22)**	**Specificity**	**Sensitivity**	**PPV**	**NPV**
HA factors			100	50	50	100
Yes	11	11				
No	0	11				
TMP-SMX resistance			72.7	100	100	88
Yes	8	0				
No	3	22				

HA = healthcare-associated, HA-MRSA = healthcare-associated methicillin resistant *S aueus*, NPV = negative predictive value, PPV = positive predictive value, TMP-SMX = trimethoprim/sulfamethoxazole.

was reported to cause clinical HA infections in respiratory care wards in Taiwan.[26] In addition, PFGE pattern F/SCC*mec* II/ST5/*spa* t002 was one of the major HA-MRSA clones in Taiwan since 2005.[25]

The sustained transmission of CA-MRSA clones into HA facilities has been a critical concern not only in Taiwan[27] but also in other regions.[28] This study indicated a higher prevalence rate of CA-MRSA by the molecular definition (66.7%) than that by the clinical definition (35.3%) because half of the patients with molecularly defined CA strains were associated with the HA factors. However, a strong correlation was still observed between the molecularly defined HA strains and the HA factors. An increasing proportion of MRSA isolates with SCC*mec* type IV in healthcare facilities was reported in the United States as well.[29] These findings might implicate that molecularly defined community strains are transmitted to health care facilities. Continuous monitoring is warranted to determine whether the HA factors are sufficient to define and distinguish between CA- and HA-MRSA isolates.

In the present study, patients with clinically defined CA-MRSA infection exhibited a higher rate of lid disorder but lower rate of keratitis than did those with clinically defined HA-MRSA infection, which were consistent with our previous study.[12] CA-MRSA has been reported to exhibit a predilection to cause nonvision-threatening infections[10,12]; therefore, patients with CA-MRSA infection could be primarily managed at outpatient clinics in our study. In addition to systemic factors, we also evaluated the local risk factors for ocular infections. It is not surprising that we found clinically defined HA-MRSA was associated with history of ocular surgery, particularly within 1 year, which was one of clinical criteria for HA-MRSA. Instead, molecularly defined HA-MRSA infection was associated with a history of ocular trauma; however, all the 4 patients had received surgical treatment and had been followed up at ophthalmology clinics for years before trauma, so they might be more exposed to HA-MRSA. Although we observed greater differences in clinical characteristics between clinically defined CA- and HA-MRSA than molecularly defined CA- and HA-MRSA, a study with a larger sample size is warranted to determine which of the 2 MRSA classifications are more suitable in predicting the clinical features and outcomes.

CA-MRSA isolates by both definitions in the present study exhibited high resistance (>80%) to clindamycin, which were different from those reported from the United States,[4,14] but were comparable with those from Taiwan.[12,30] In Taiwan, CA-MRSA also exhibited multidrug resistance. Susceptibility differed only for TMP-SMX; CA-MRSA isolates were significantly more susceptible than HA-MRSA isolates.

Two national surveys of ocular isolates conducted in the United States reported a resistance rate of >80% to fluoroquinolones for MRSA[18,31]; however, these studies did not provide any further classification of the MRSA isolates. Recently, a Chinese study by Hong et al reported that clinically defined CA-MRSA exhibited a significantly higher susceptibility to fluoroquinolones than HA-MRSA (61.1%–87% vs 32.9%–63.7%)[32] and a US study by Hesje et al reported that 37.5% of SCC*mec* type IV (molecularly defined CA-MRSA), but no SCC*mec* type II, (molecularly-defined HA-MRSA) isolates were susceptible to fluoroquinolones.[14] In the present study, the rate of susceptibility to the 4 tested fluoroquinolones was significantly higher for CA-MRSA than for HA-MRSA, particularly by the molecular definition (all $P < 0.001$). All the isolates of CC 59, the most common CA-MRSA strains in Taiwan, were susceptible to fluoroquinolones, whereas >70% of the molecularly defined HA-MRSA isolates were resistant to fluoroquinolones. These findings suggested that distinguishing HA- from CA-MRSA isolates, particularly by genotyping, is crucial to guide the treatment of patients with MRSA ocular infection because CA-MRSA plays an essential role in ocular infections,[12] and fluoroquinolones are the most popular empiric antibiotics prescribed by ophthalmologists. Unfortunately, the susceptibility of fluoroquinolones is not included in the recommended testing panel of antibiotics for *S aureus* proposed by the CLSI and thus is not performed routinely in some microbiological laboratories such as ours, not to mention genotyping, a time-consuming and clinician-unfriendly procedure.

To help the ophthalmologists to predict molecular characteristics of clinical MRSA isolates, we proposed 2 potential differential tools in the present study: one was HA criteria, related to the patient's epidemiologic characteristics; the other was the resistance of TMP-SMX, related to phenotype of the isolates. Both tools had a high negative predictive value and the latter had even a high positive predictive value. Simply speaking, we may prescribe fluoroquinolones to treat MRSA ocular infection without the concern of resistance when the patient has no HA factors. However, when one or more HA factors are identified, the possibility of fluoroquinolones resistance should be considered (50% resistance), particularly the isolates are resistant to TMP-SMX (100% resistance).

There are some limitations in the present study. Although we prospectively collected the specimens, we retrospectively reviewed the clinical data; some risk factor assessment might be

incomplete. Relatively small sample size would affect the analysis of statistical significance, but a few differences between CA- and HA-MRSA were still observed. In addition, the in vitro susceptibility based on the serum systemic standards does not always correlate with clinical response because there are no susceptibility standards for topical therapies. As with different microbiological characteristics in different geographic areas, the findings of the present study should not be generalized to other regions or populations.

In conclusion, for ocular MRSA infections in Taiwan, CC59 with SCC*mec* IV/V_T was the predominant CA clone, whereas CC239 with SCC*mec* III/III_A was the predominant HA clone. Despite the strong correlation between the HA factors and the molecular HA strains, transmission of CA strains to healthcare facilities was observed. We also found a relatively high susceptibility of molecularly defined CA-MRSA strains to fluoroquinolones. HA factors as well as susceptibility to TMP-SMX could be used as predictive tools for molecular characteristics of MRSA strains. Accordingly, with the help of these tools, ophthalmologists can prescribe more appropriate antibiotic treatments and indirectly improve the prognosis of patients with MRSA ocular infection.

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