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Vancomycin, teicoplanin, daptomycin, and linezolid MIC creep in methicillin-resistant *Staphylococcus aureus* is associated with clonality

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Abstract

The purpose of this study is to evaluate the susceptibility trend of vancomycin, teicoplanin, daptomycin, and linezolid against methicillin-resistant *Staphylococcus aureus* (MRSA) blood isolates of different clones over an 11-year period.

From 2000 to 2010, all bloodstream MRSA isolates from Chang Gung Memorial Hospital in Taiwan were prospectively collected. Three periods, namely 2000 to 2001, 2004 to 2005, and 2010, were included and 124 MRSA isolates were selected from each period. Minimum inhibitory concentrations (MICs) were determined by E-test. All the isolates were molecularly characterized.

MRSA molecular epidemiology evolved from 1 predominant pulsotype (type A) to 5 major pulsotypes of 3 clonal complexes (CC). Vancomycin, teicoplanin, and daptomycin MICs creep were observed, particularly for pulsotype A-CC 239-staphylococcal cassette chromosome *mec* (SCC*mec*) III though its prevalence dramatically decreased since 2004 to 2005. Throughout the study period, the overall vancomycin modal MIC was stable at 1.5 mg/L, but teicoplanin and linezolid modal MIC increased to 2 and 2 mg/L, respectively. Isolates with teicoplanin and linezolid ≧2 ug/mL belonged to multiple clones. Pulsotype F-ST5-SCC*mec* II with a high rate of teicoplanin MIC ≧2 ug/mL continued clonal spread. Teicoplanin MIC had a high correlation with linezolid MIC.

Molecular epidemiology MRSA bloodstream isolates in northern Taiwan evolved from 2000 throughout 2010, which was subsequently associated with the changing distribution of antibiotic MICs. While vancomycin MIC level remained unchanged, teicoplanin, daptomycin, and linezolid MIC levels increased. The impact of these changes on clinical treatment response deserves further investigations.

Abbreviations: CC = clonal complexes, MIC = minimum inhibitory concentrations, MRSA = methicillin-resistant *Staphylococcus aureus*, SCCmec = staphylococcal cassette chromosome mec.

Keywords: linezolid, methicillin-resistant *Staphylococcus aureus*, minimum inhibitory concentration, teicoplanin, vancomycin

1. Introduction

Staphylococcus aureus can cause a broad spectrum of infections, including bacteremia, endocarditis, pneumonia, osteoarticular infections, and skin and soft tissue infections. In 1961, methicillin-resistant *Staphylococcus aureus* (MRSA) was firstly detected in the United Kingdom[1]; since then MRSA rapidly spread worldwide and drew much concern because it gave rise to serious problems in either hospital settings or later community.

MRSA strains are generally concentrated into a subset of clones. These clones have themselves evolved to be successful in adapting to antibiotic selective pressure and disseminated worldwide.[2] For decades, glycopeptides (vancomycin or teicoplanin) have been the mainstay for the treatment of serious MRSA infections. However, recently, an increase in the distribution of higher vancomycin minimum inhibitory concentration (MIC) values but within the susceptibility range proposed by the Clinical and Laboratory Standards Institute, so-called MIC creep, among MRSA isolates has raised serious concern because patients infected by these MRSA isolates are less responsive to vancomycin. MRSA isolates with a vancomycin MIC value, as well as teicoplanin MIC value, >1.5 mg/L were associated with a higher rate of treatment failure and a higher mortality rate.[3–5]

In Taiwan, in 2000, most MRSA isolates (around 70%) shared common molecular characteristics, a particular pulsotype (type A) with sequence types (ST) 239 or 241 carrying SCC*mec* III.[6] Ten years later (in 2010), the molecular epidemiology of MRSA has evolved to be more diverse and there are 3 major clones identified, namely clonal complex (CC) 239, CC59, and CC5, in the hospital settings.[7] However, the details of clinical MRSA isolates to common antimicrobials susceptibility in terms of MICs were not

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described. The aim of this study was to evaluate the susceptibility trend of glycopeptides (vancomycin, teicoplanin), daptomycin, and linezolid against various MRSA clones over the last 11 years.

2. Materials and methods

2.1. Ethics statement

The institutional review board of Chang Gung Memorial Hospital approved this study. A waiver of consent was granted given the retrospective nature.

2.2. Study design, setting, and patient selection

This cohort study was conducted at Chang Gung Memorial Hospital-Linkou. This 3700-bed university-affiliated teaching hospital provides both primary and tertiary care in northern Taiwan. All MRSA bloodstream isolates from 2000 throughout 2010 were prospectively collected. Three time periods were arbitrarily selected, including July 2000 to June 2001, July 2004 to June 2005, and 2010. From each period, 124 MRSA isolates each were selected (1 per 10 to 1 per 5 consecutive isolates depending on the isolate number size). Only 1 isolate was selected from a single patient. In total, 372 isolates were included for analysis. All isolates were identified as *Staphylococcus aureus* according to standard methods, and cefoxitin susceptibility was assessed by the disc diffusion method.[8] *S. aureus* ATCC 29213 was used as a control strain. The patient data including in-hospital mortality, hospitalization length, bacteremia duration, and focus of bacteremia were recorded from the medical records. The duration of bacteremia was defined as the date of first positive MRSA culture subtracted from the date of first negative culture for all patients for whom this information was available.

2.3. Antimicrobial susceptibility tests

MICs of the isolates to 4 antibiotics, including vancomycin, teicoplanin, linezolid, and daptomycin, were determined by E-test (AB BIODISK, Solna, Sweden) according to the manufacturers' instructions. *S. aureus* ATCC 29213 was used as a control strain with every set of tests.

2.4. Etest glycopeptide resistance detection

Screening for heterogeneous resistance to vancomycin (hVISA) was done in parallel by the glycopeptide resistance detection (GRD) methods according to the manufacturer's instructions (bioMe'rieux SA, Lyon, France).

2.5. Molecular typing

Pulsed-field gel electrophoresis (PFGE) was carried out according to the method described previously.[6,9] Strains with 4 or more different bands were considered different and were assigned to separate types. The genotypes were labeled following our previous studies in an alphabetical order.[6,9,10] Staphylococcal chromosome cassette mec (SCC*mec*) typing was performed via a multiplex PCR mentioned previously.[11] Multilocus sequence typing (MLST) was performed for selective strains of each major PFGE type according to the method provided in the MLST Web site (http://www.mlst.net).

2.6. Statistical analysis

Categorical variables were examined using the χ^2 or Fisher exact tests, including the percentage of clinical MRSA isolates stratified by PFGE pattern, percentage of MIC changes during 3 time periods, the association between clonality and MIC changes, in-hospital mortality, primary sites of infections caused by the different clonal complex types. Length of hospital stays and bacteremia duration were compared by 1-way analysis of variance. Spearman rank-correlation coefficients were calculated for tests of correlation between MICs of various antibiotics. The statistical analyses were performed via SAS statistical software (version 9.1; SAS Institute Inc., Cary, NC, USA). A P value less than 0.05 was considered statistically significant.

3. RESULTS

3.1. Molecular characteristics of MRSA isolates

The distribution of PFGE patterns, SCC*mec* types, and MLST of all isolates are shown in Table 1. Ninety-two percent of the isolates clustered in 3 clonal complexes (CC), namely CC239 (sequence type 239 and its variants), CC59, and CC5. There were 2 pulsotypes identified for CC239, namely types A and B. Pulsotype A/SCC*mec* III accounted for 78% of the isolates in 2000 to 2001, but significantly decreased to 30.6% in 2004 to 2005, and 30.6% in 2010 ($P<0.001$). The proportion of the isolates of pulsotytype B significantly fluctuated between 2.4% in 2000 to 2001, 12.1% in 2004 to 2005, and 5.6% in 2010 ($P = 0.007$). There were 2 pulsotypes identified for CC59, namely

Table 1

Distribution of molecular characteristics of 372 methicillin-resistant *Staphylococcus aureus* bloodstream isolates during study period, stratified by pulsed-field gel electrophoresis (PFGE) patterns.

PFGE pattern	Total no. (%)	2000–2001 no. (%)	2004–2005 no. (%)	2010 no. (%)	*P* value	MLST type (s)*	SCCmec type (s) (no.)
A	173 (46.5)	97 (78.2)	38 (30.6)	38 (30.6)	<0.001	239 (7/8), 241 (1/8)	III (134), IIIA (38), IIIB (1)
B	25 (6.7)	3 (2.4)	15 (12.1)	7 (5.6)	0.007	239 (2/3), 241 (1/3)	III (20), IIIA (3), IIIB (1), IV (1)
C	59 (15.8)	18 (14.5)	20 (16.1)	21 (16.9)	0.9	59 (5/5)	II (1), IV (58), VT (1)
D	27 (7.3)	3 (2.4)	13 (10.5)	11 (8.9)	0.04	59 (4/4)	IV (4), VT (23)
F	44 (11.8)	1 (0.8)	16 (12.1)	27 (21.8)	<0.001	5 (4/4)	II (43)
AH	14 (3.8)	0 (0.0)	14 (11.3)	0 (0.0)	<0.001	5 (1)	II (14)
BM	6 (1.6)	0	0	6 (4.8)	0.004	45 (1)	III (2), IIIA (1),IV (1)
other	24 (6.5)	2 (1.6)	8 (6.5)	14 (11.2)	0.01	1 (1/10), 5 (2/10), 30 (2/10), 59 (3/10), 72 (1/10), 508 (1/10)	II (2), IV (21), VT (1)

MLST = multilocus sequence type, SCCmec = staphylococcal chromosome cassette.

* Numbers in parentheses represent no. of isolates with this MLST type/no. with this PFGE pattern that underwent MLST analysis.

types C and D. The activity of pulsotype C/SCC*mec* IV was steady, around 14.5% to 16.9% of isolates, during the study period. Pulsotype D /SCC*mec* V_T or IV had a tendency to increase from 2.4% in 2000 to 2001 to 8.9% in 2010 ($P=0.04$). There were also 2 pulsotypes identified for CC5, namely type F and AH. Pulsotype F/SCC*mec* II emerged from 0.8% in 2000 to 2001 to 21.8% in 2010, being the second large clone in 2010 ($P<0.001$). Pulsotype AH accounted for 12.1% of the isolates in 2004 to 2005, but was not detected in other 2 periods. Pulsotype BM/ST45/ appeared in 2010 and accounted for 4.8% of all isolates in 2010.

3.2. Antimicrobial susceptibilities

All isolates were susceptible to vancomycin, teicoplanin, and linezolid based on Clinical and Laboratory Standards Institute breakpoints. 3.2% of the isolates were not susceptible to daptomycin. During the study period, only vancomycin MIC_{90} remained steady as 2 ug/mL. While MIC_{90} of teicoplanin increased from 2 ug/mL in 2000 to 2001 to 3 ug/mL in 2010, MIC_{90} of daptomycin increased from 0.38 ug/mL in 2000 to 2001 to 1 ug/mL in 2010, and MIC_{90} of linezolid increased from 1.5 ug/mL in 2000 to 2001 to 2 ug/mL in 2010. Figure 1 shows the distribution of MICs of MRSA isolates to 4 antibiotics, including vancomycin, teicoplanin, linezolid, and daptomycin. The frequency of MRSA isolates with vancomycin MIC ≥2 ug/mL was around 21% to 25% throughout the study period. But the frequency of MRSA isolates with teicoplanin MIC ≥2 ug/mL significantly increased from 29.8% in 2000 to 2001 to 60.5% in 2004 to 2005, and 51.6% in 2010 ($P<0.001$). The frequency of MRSA isolates with linezolid MIC ≥ 2 ug/mL increased from 4.0% in 2000 to 2001 to 64.5% in 2004 to 2005 and 43.5% in 2010 ($P<0.001$). The frequency of MRSA isolates with daptomycin MIC ≥ 1 ug/mL also significantly increased from none in 2000 to 2001 to 2.4% in 2004 to 2005 and 12.1% in 2010 ($P<0.001$).

3.3. Association between clonality and vancomycin, teicoplanin, daptomycin, and linezolid MIC change

Figure 2 shows the distribution of MICs of MRSA isolates to 4 antibiotics, including vancomycin, teicoplanin, linezolid, and daptomycin, stratified by pulsotypes and time periods. Although there was no vancomycin MIC creep during the study period, both the percentages of pulsotype A/CC239 isolates with vancomycin MIC ≥ 2 ug/mL and teicoplanin MIC ≥ 2 ug/mL increased significantly throughout the study period ($P<0.01$). The percentage of pulsotype B/CC239 isolates with linezolid MIC ≥ 2 ug/mL also increased significantly from none in 2000 to 2001, 33.3% in 2004 to 2005 to 57.1% in 2010 ($P<0.001$). Most isolates (8/15) with daptomycin MIC > 1 ug/mL belonged to pulsotype A/CC239 and appeared in 2010 ($P<0.001$). The percentage of pulsotype F/CC5 isolates with teicoplanin MIC ≥ 2 ug/mL remained high (>80%) throughout the study period. GRD was performed on 44 isolates of pulsotype F/CC5, which showed 27 of them (61.4%) were hVISA. Reduced susceptibility to teicoplanin over time among isolates of pulsotype F/CC5 was largely due to hVISA.

Isolates with both teicoplanin and linezolid MIC ≥ 2 mg/L belonged to multiple clones of which pulsotype A/CC239 and pulsotype F/ST5 were the 2 major clones (Fig. 3).

3.4. Correlation of glycopeptide (Vancomycin and Teicoplanin) MICs with those of daptomycin and linezolid

Vancomycin MIC value was significantly correlated with both teicoplanin ($r=0.31$; $P<0.001$) and daptomycin MICs ($r=0.26$; $P<0.001$), but not with linezolid MIC ($r=-0.04$; $P=0.45$). Teicoplanin MIC value was significantly correlated with both daptomycin ($r=0.36$; $P<0.001$) and linezolid MICs ($r=0.31$; $P<0.001$). There was no correlation between daptomycin MIC and linezolid MIC ($r=0.06$; $P=0.2$).

3.5. Clinical features and outcomes

Among 5 major clonal complex types, pulsotype A/CC239 was significantly associated with highest in-hospital mortality (54.7%) compared with other types (Table 2). Length of hospital stays and bacteremia duration were not different between 5 clonal complex types. With regard to primary sites of infections, pulsotype A/CC239 had highest rate of lower respiratory tract infection (39.3%) compared with other types (Table 2).

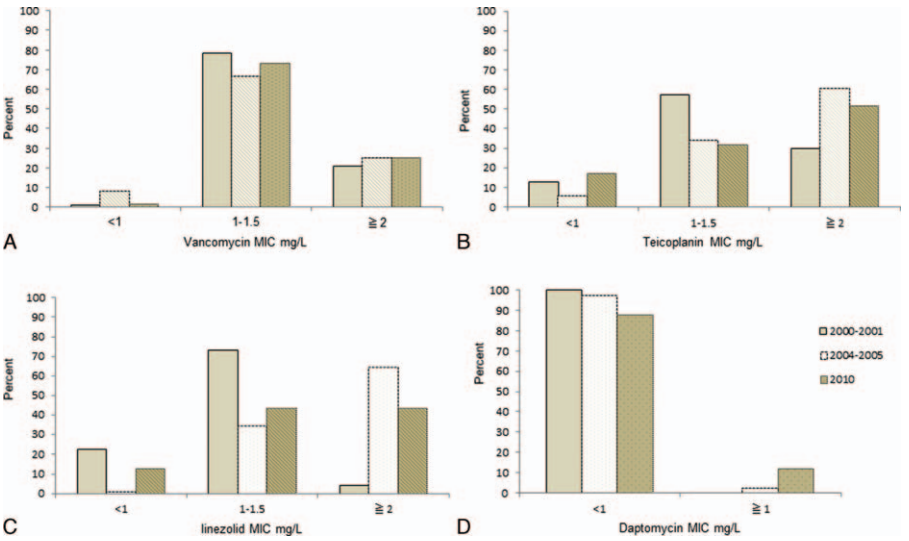

Figure 1. Distribution of MRSA MICs for (A) vancomycin, (B) teicoplanin, (C) linezolid, (D) daptomycin during 2000 to 2001, 2004 to 2005, and 2010. MIC = minimum inhibitory concentrations, MRSA = methicillin-resistant *Staphylococcus aureus*.

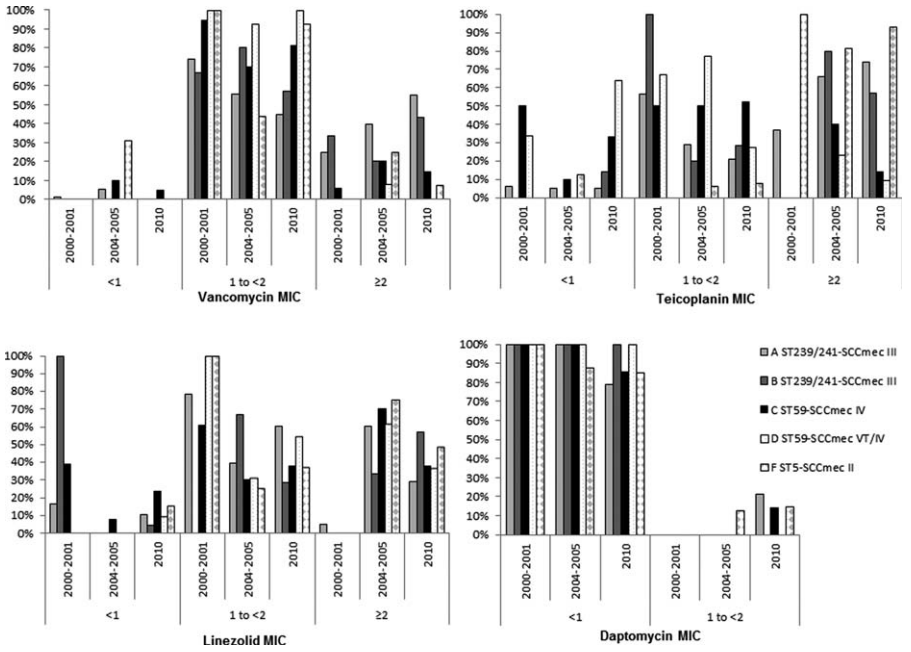

Figure 2. Trend in distribution of antibiotic minimal inhibition concentration (MIC, mg/L) levels of 372 methicillin-resistant *Staphylococcus aureus* bloodstream isolates from 2000 to 2010, stratified by pulsed-field gel electrophoresis (PFGE) patterns. MIC = minimum inhibitory concentrations.

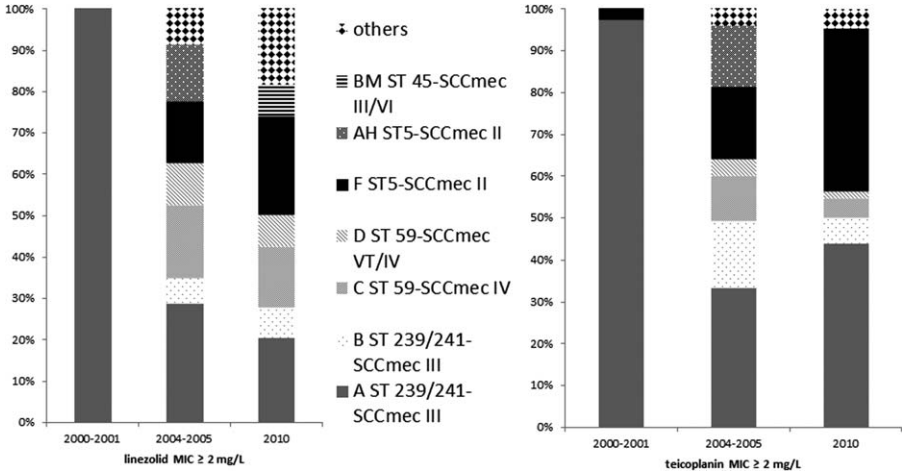

Figure 3. Distribution of MRSA major clones among isolates with teicoplanin and linezolid MIC ≧ 2 mg/L during 2000 to 2001, 2004 to 2005, and 2010. MIC = minimum inhibitory concentrations, MRSA = methicillin-resistant *Staphylococcus aureus*.

Table 2

In-hospital mortality, length of hospital stay, bacteremia duration, and primary sites of infections caused by different clonal complex types.

	Pulsed-field gel electrophoresis (PFGE) patterns, no (%)					
	A/CC239 (117)	B/CC239 (24)	C/CC59/ (45)	D/CC59 (24)	F/CC5 (43)	*P* value
In-hospital mortality, no., %	64 (54.7)	10 (41.7)	15 (33.3)	5 (20.8)	17 (39.5)	0.007
Length of hospital stay after bacteremia (d), median (range)	18 (1–1391)	22 (10–125)	16 (1–149)	20 (1–96)	24 (4–354)	0.7
Bacteremia duration (d), median (range)	9 (2–124)	9 (1–24)	7 (1–23)	12 (1–38)	11 (2–55)	0.7
Primary sites of infections						
Vascular device related	25 (21.4)	4 (16.7)	11 (24.4)	3 (12.5)	14 (32.6)	0.3
Skin and soft tissue infection	20 (17.1)	6 (25)	13 (28.9)	6 (25)	8 (18.6)	0.5
Lower respiratory tract infection	46 (39.3)	9 (37.5)	7 (15.6)	6 (25)	16 (37.2)	0.04
Orthopedic infection	10 (8.5)	1 (4.2)	1 (2.2)	4 (16.7)	2 (4.7)	0.2
Others*	16 (13.7)	4 (16.7)	13 (28.9)	5 (20.8)	3 (7.0)	0.06

* Others include urinary tract infection, peritonitis, meningitis, epididymitis, and no focus identified.

4. Discussion

Results from the present study indicated that the molecular epidemiology of MRSA bloodstream isolates changed markedly in our hospital in the past decade. From 2000 to 2010, we observed that CC239 significantly decreased; instead, ST5 and ST45 significantly increased, while CC59 remained relatively steady. These results were consistent with a recent island-wide study.[7] In this study, MIC creep was noted for daptomycin, teicoplanin, and linezolid but not for vancomycin, which was only noted for the isolates of pulsotype A/CC239. Furthermore, most isolates of pulsotype F/ST5 had both teicoplanin and linezolid MICs ≧ 2 ug/mL.

In this study, we found a specific clone, pulsoype A/CC239, with a significant vancomycin and teicoplanin MIC creep but with a reduced prevalence. It seemed that the reduced prevalence of this clone since 2004 to 2005 made the overall MIC creep for vancomycin undetected and for teicoplanin less obvious. Decreased prevalence of pulsotype B/CC239 which presented with linezolid MIC creep also made the overall linezolid MIC creep less obvious.

MRSA CC239 is considered a healthcare-associated MRSA and spreads globally, including Asia.[12,13] In this study, we found that the prevalence of pulsotype A/CC239 significantly decreased from 2000 throughout 2010 in our hospital, but MIC creep was noted for vancomycin, teicoplanin, and daptomycin. Theoretically, multiple antibiotics resistance might bring fitness burden for this clone and subsequently promoted its transmission and survival advantage in the environment. The issue why the clone of CC239 lost its predominance in our hospital as well as the whole island needs to be clarified.

Pulsotype F/ST5/SCC*mec* II is also an epidemic clone and has been found to spread in Japan, the United States, the United Kingdom, Finland, and Ireland.[14,15] Since 2004 to 2005, this clone became one of the major clones in hospital settings in Taiwan.[16,17] In this study, we found that isolates of this clone had an extremely high rate (>80%) of teicoplanin MIC ≧ 2 ug/mL throughout the study period and continued clonal spread. Of note, 61.4% of them were hVISA. Infections caused by hVISA were usually associated with vancomycin treatment failure.[18]

Both vancomycin and teicoplanin are potent glycopeptides active against MRSA. Previous studies have shown that teicoplanin was as efficacious as vancomycin in terms of treatment success rate for health care-associated MRSA bacteremia.[19,20] Like vancomycin, area under the curve (AUC)/MIC ratio is the best predictor of clinical response for teicoplanin and linezolid therapy in serious MRSA infections. Increases in the teicoplanin and linezolid MICs, although remaining within the susceptible range, may affect the attainable pharmacodynamics exposure necessary to reach a bactericidal effect. A study in Brazil showed that teicoplanin 800 mg every 24 hours and linezolid 600 mg every 24 hours can achieve >90% target attainment for isolates with MICs up to 1 mg/L.[21] If the MIC increases to 2 mg/L, the rate of target attainment declines to about 50% for teicoplanin and 60% for linezolid.[21] It was coherent with a previous study, in which a higher teicoplanin MIC value (>1.5 mg/L) was an independent risk factor for treatment failure among teicoplanin-treated MRSA bacteremic patients.[4] In this study, nearly half of the isolates collected in 2010 in our hospital had teicoplanin and linezolid MICs > 2 mg/L. High teicoplanin doses are needed to rapid attain a higher Cmin by appropriate antibiotic loading.[22] Alternatively, daptomycin (8–10 mg/kg) alone or in combination with either gentamicin, rifampin, linezolid, trimethoprim/sulfamethoxazole, or a ß-lactam antibiotic can be considered for persistent MRSA bacteremia.[23]

In addition, the present study also indicated a high correlation between teicoplanin MIC and linezolid MIC of MRSA isolates, but not between vancomycin MIC and linezolid MIC. The findings may be included for the consideration of choosing the alternative antiMRSA medications for patients with teicoplanin treatment failure. However, the issue whether cross-resistance existed between teicoplanin and linezolid in MRSA isolates needs further studies.

There are several limitations in the present study. First, we used E test GRD to detect hVISA, which has good specificity but limited sensitivity.[24] Second, we did not review and correlate clinical responses and the patients' severity of comorbidities with antimicrobial MIC levels. Third, we did not correlate the antimicrobial daily dosages per patient during the study period in our hospital with the change of antimicrobial MIC levels. Fourth, this study was conducted in a single medical center in Taiwan, so the issue whether the results presented in this report can be generalized to other institutes needs further evaluation.

Given the trend of increased teicoplanin and linezolid MIC with polyclonal dissemination, it is essential to meticulously monitor the adequate usage of teicoplanin and continuously investigate the evolving MRSA molecular epidemiology.

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