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ORIGINAL ARTICLE

In vitro activity of linezolid, tigecycline, and daptomycin on methicillin-resistant *Staphylococcus aureus* blood isolates from adult patients, 2006—2008: Stratified analysis by vancomycin MIC

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Background: The recent molecular epidemiological studies concerning epidemiological studies concerning methicillin-resistant *Staphylococcus aureus* (MRSA) blood isolates from adult patients and susceptibilities of MRSA isolates with high vancomycin minimum inhibitory concentrations (MICs) ($\geq$2 mg/L) to linezolid, tigecycline, and daptomycin in Taiwan remain limited. The objectives of the study were (1) to better understand the change of molecular epidemiology of MRSA blood isolates and (2) to evaluate the *in vitro* activity of new anti-Gram-positive agents, including linezolid, tigecycline, and daptomycin.

Methods: A total of 470 nonduplicate MRSA blood isolates from adult patients (older than 18 years) were collected from January 2006 to December 2008. The MICs of these isolates to various antibiotics were determined. Multilocus sequence typing was also performed in all isolates.

Results: Three sequence types (STs) constitute most (92.1%) of these 470 MRSA isolates: ST239 (53.2%), ST59 (23.2%), and ST5 (15.7%). Throughout the 3-year study, the ST239 strain remained predominant but with a significant trend of declining annually ($p = 0.03$). In contrast, the proportion of isolates of ST59 increased, although the increment was insignificant ($p = 0.14$). The proportion of MRSA isolates with a vancomycin MIC of 2 mg/L was 17.2%. All of these isolates with a vancomycin MIC of 2 mg/L were susceptible to linezolid and tigecycline, whereas most of them (98.8%) were susceptible to daptomycin.

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Conclusions: ST239 remained predominant during the 3-year period but with a significant trend of declining. Moreover, linezolid, tigecycline, and daptomycin remained highly active against MRSA blood isolates, even with a vancomycin MIC of 2 mg/L.

Introduction

The high prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA), accounting for up to 80% of all *S. aureus* causing nosocomial infection, has been noted in Taiwan since 1998.[1] Owing to the high transmissibility of MRSA,[2] increased prevalence of MRSA infections might result from the spread of the predominant endemic strains.[3] Previous studies had demonstrated a predominant MRSA strain within an institute, although it might change over the years; in addition, different MRSA strains would have different antibiograms.[4–6] Several studies have also reported that the expanding community reservoirs of community-associated MRSA (CA-MRSA) had inevitably led to the invasion of CA-MRSA strains into hospitals; in addition, CA-MRSA strains may be replacing the traditional health care–associated MRSA (HA-MRSA) strains in the health care–associated infections.[7–9]

Among the clinical problems caused by MRSA, bloodstream infection has received considerable attention owing to its relatively high morbidity and mortality rates. Although vancomycin has been served as the cornerstone of treatment against serious MRSA infections in the past decades, bacteremia and endocarditis caused by MRSA cannot always be easily treated by vancomycin.[2] Moreover, several studies demonstrated an increased clinical failure of the vancomycin therapy in patients with MRSA bacteremia, especially when the causative isolate had a higher vancomycin minimum inhibitory concentration (MIC) ($\geq$2 mg/L).[10,11] Under such clinical circumstances, newer antimicrobial agents, for example, linezolid, tigecycline, and daptomycin, have been used as alternatives to vancomycin.[12,13] However, susceptibilities of MRSA isolates with high vancomycin MICs ($\geq$2 mg/L) to linezolid, tigecycline, and daptomycin, have not been thoroughly analyzed in Taiwan. The objectives of the study were (1) to better understand the change of molecular epidemiology of MRSA blood isolates and (2) to evaluate the *in vitro* activity of linezolid, tigecycline, and daptomycin, against MRSA isolates with high vancomycin MICs ($\geq$2 mg/L).

Methods

Bacterial isolates and definition

This study was performed at the National Taiwan University Hospital, a major teaching hospital located in northern Taiwan with a bed capacity of 2,200. Totally, 470 non-duplicate blood isolates of MRSA from adult patients, older than 18 years, were collected between January 2006 and December 2008. All isolates were stored at −70°C until the subsequent microbiological tests were performed.

HA-MRSA infections were defined as the presence of any of the following risk factors: (1) an MRSA infection identified after 48 hours of admission; (2) a previous hospitalization, surgery, dialysis, or residence in a long-term-care facility within 1 year of the MRSA culture date; (3) the presence of a permanent indwelling catheter or percutaneous medical device (e.g. tracheostomy tube, gastrostomy tube, nephrostomy tubes, or biliary drains) at the time of positive culture; or (4) a known previous positive culture for MRSA within 1 year of the study period.[14,15] Community-onset MRSA (CO-MRSA) infection was defined as an illness compatible with staphylococcal disease, in which MRSA was recovered from the culture of specimens obtained from the site of infection in an outpatient setting or from an inpatient within 48 hours of admission.[16] CA-MRSA infections were defined by a community-onset infection in the absence of any of the aforementioned health care–associated risk factors.[16] The causative MRSA isolates of CA-MRSA infections were defined as CA-MRSA isolates. Conversely, the causative MRSA isolates of HA-MRSA infections and CO-MRSA infections were defined as HA-MRSA isolates and CO-MRSA isolates, respectively.

Antimicrobial susceptibility tests

The susceptibilities of these isolates to various antibiotics, including erythromycin, clindamycin, minocycline, trimethoprim–sulfamethoxazole (SXT), gentamicin, vancomycin, linezolid, and tigecycline, were determined using the agar dilution method based on the guidelines of the Clinical and Laboratory Standards Institute.[17] The susceptibility to daptomycin was determined by the broth microdilution method.[17] The susceptibilities of erythromycin, clindamycin, minocycline, SXT, gentamicin, ciprofloxacin, vancomycin, linezolid, and daptomycin were interpreted according to the Clinical and Laboratory Standards Institute breakpoints.[18] The susceptibility to tigecycline was determined based on the recommended breakpoints by the European Committee for Antimicrobial Susceptibility Testing.[19] A breakpoint less than or equal to 0.5 mg/L was determined to be tigecycline susceptible.[19] *Staphylococcus aureus* ATCC 29213 was used as the internal control for each run of the susceptibility test.

Molecular typing

Preparation of chromosomal DNA was described previously.[19] All isolates were tested by staphylococcal cassette chromosome *mec* (SCC*mec*) element typing and multilocus sequence typing.[20]

Statistical analysis

The Chi-squared test for trend was used to test the secular change. The statistical analyses were performed using SAS

Table 1 The characteristics of the 470 MRSA blood isolates stratified by either infection types or STs

Characteristics	Origin, *n* (%)				Clonal type, *n* (%)	
	HA-MRSA	CO-MRSA	CA-MRSA	ST239	ST59	ST5
Total isolates	337 (71.7)	124 (26.4)	9 (1.9)	250 (53.2)	109 (23.2)	74 (15.7)
SCC*mec* type						
II	59 (17.5)	14 (11.3)	0	0	0	74 (100)
III	204 (60.5)	50 (40.3)	0	250 (100)	0	0
IV	50 (14.8)	35 (28.2)	6 (66.7)	0	65 (59.6)	0
V	24 (7.1)	25 (20.2)	3 (33.3)	0	44 (40.4)	0
Susceptible to						
Erythromycin	14 (4.2)	17 (13.7)	1 (11.1)	0	10 (9.2)	0
Clindamycin	15 (4.5)	21 (16.9)	2 (22.2)	1 (0.4)	12 (11.0)	0
Minocycline	145 (43.0)	69 (55.6)	9 (100)	20 (8.0)	103 (94.5)	70 (94.6)
SXT	129 (38.3)	72 (58.1)	9 (100)	3 (1.2)	105 (96.3)	72 (97.3)
Gentamicin	47 (13.9)	43 (34.7)	5 (55.6)	4 (1.6)	79 (72.5)	4 (5.4)
Ciprofloxacin	66 (19.6)	53 (42.7)	9 (100)	1 (0.4)	104 (95.4)	0

CA-MRSA = community-associated MRSA; CO-MRSA = community-onset MRSA; HA-MRSA = health care–associated MRSA; MRSA = methicillin-resistant *Staphylococcus aureus*; PVL = Panton–Valentine leukocidin; SCC*mec* = staphylococcal cassette chromosome *mec*; ST = sequence type; SXT = trimethoprim–sulfamethoxazole.

statistical software (version 9.1; SAS Institute Inc., Cary, NC, USA). A p value less than 0.05 was considered significant.

Results

Characteristics, molecular typing, and antibiograms

Among the 470 tested MRSA isolates, 337 (71.7%), 124 (26.4%), and 9 (1.9%) were classified into HA-MRSA, CO-MRSA, and CA-MRSA isolates, respectively. Table 1 summarizes the distribution of SCC*mec* element, and multilocus sequence typing among the 470 isolates. The Type III SCC*mec* element was the predominant element among HA-MRSA (60.5%) and CO-MRSA (40.3%) isolates. However, 66.7% and 33.3% of CA-MRSA isolates carried the Type IV and the Type V SCC*mec* elements, respectively.

Three sequence types (STs) constituted most of the 470 MRSA isolates (92.1%)—ST239 (53.2%), ST59 (23.2%), and ST5 (15.7%). Similarly, three STs accounted for most of the 337 HA-MRSA isolates (93.8%)—ST239 (58.8%), ST59 (17.8%), and ST5 (17.2%). Among the nine CA-MRSA isolates, eight (88.9%) were ST59 and one (11.1%) was ST8. All ST239 isolates (100%) carried the Type III SCC*mec* element. In contrast, all ST5 isolates (100%) carried the Type II SCC*mec* element. Sixty-five (59.6%) and 44 (40.4%) isolates of ST59 carried the Type IV and the Type V SCC*mec* elements, respectively.

Most of the CA-MRSA isolates expressed resistance to both erythromycin and clindamycin, but were susceptible to minocycline, SXT, and ciprofloxacin. However, most HA-MRSA isolates were multidrug resistant. Almost all ST59 and ST5 isolates were susceptible to minocycline and SXT, but resistant to erythromycin and clindamycin. Interestingly, although almost all ST59 isolates were also susceptible to ciprofloxacin, all ST5 isolates were resistant to ciprofloxacin. Gentamicin susceptibility rates of ST59 and ST5 isolates were 72.5% and 5.4%, respectively. With regard to ST239 isolates, almost all strains were resistant to erythromycin, clindamycin, minocycline, SXT, gentamicin, and ciprofloxacin.

Change in the proportion of ST239, ST59, and ST5, from 2006 to 2008

Figure 1 demonstrates the change in the proportion of ST239, ST59, and ST5 isolates among the tested 470 MRSA blood isolates. The proportion of ST5 isolates remained stable ($p = 0.77$). Conversely, although the proportion of ST59 isolates increased during the 3-year period (20.3–27.2%), the increment was not statistically significant ($p = 0.14$). Interestingly, although ST239 isolates remained dominant, the proportion of ST239 isolates declined significantly from 2006 to 2008 ($p = 0.03$). As for the HA-MRSA isolates, Fig. 2 shows the changes in the proportions of ST239, ST59, and ST5, during the study period. Among the HA-MRSA isolates, the proportion of ST239 declined significantly ($p = 0.007$);

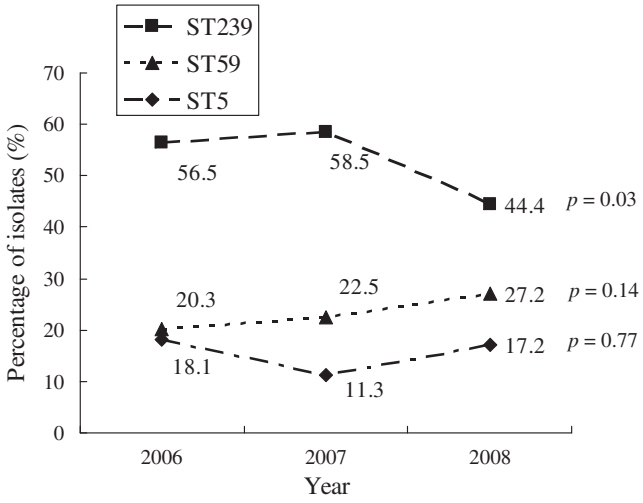

Figure 1. The change in the proportion of ST239, ST59, and ST5, among 470 methicillin-resistant *Staphylococcus aureus* blood isolates, 2006–2008. ST = sequence type.

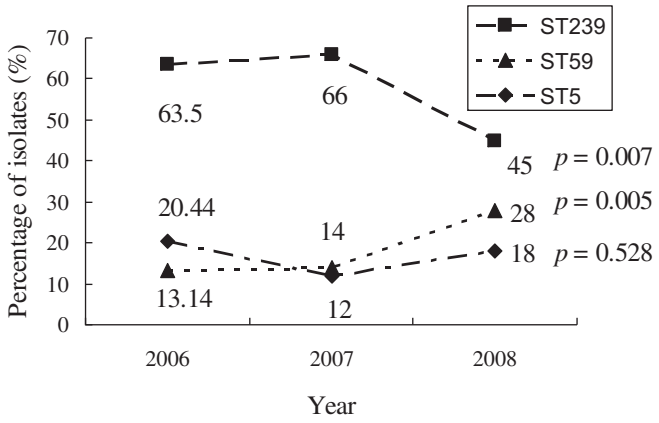

Figure 2. The change in the proportion of ST239, ST59, and ST5, among health care—associated methicillin-resistant *Staphylococcus aureus* isolates, 2006—2008. ST = sequence type.

concurrently, the proportion of ST59 increased significantly ($p = 0.005$). Similarly, the proportion of ST5 did not change during the 3-year period.

Relationship between specific STs and vancomycin MICs

Although all 470 isolates were susceptible to vancomycin (MIC range, 0.5—2 mg/L), 81 isolates (17.2%) had a vancomycin MIC of 2 mg/L. Most (65.5%) of the MRSA isolates with a vancomycin MIC of 0.5 mg/L belonged to ST59, whereas ST239 and ST5 isolates only accounted for 6.9% and 10.3%, respectively. Among 81 MRSA isolates with a vancomycin MIC of 2 mg/L, 73 (90.1%) belonged to ST239, whereas only six, one, and one belonged to ST5, ST8, and ST241, respectively. This finding implies that a higher proportion of MRSA blood isolates with increased MICs (2 mg/L) of vancomycin in this study may be because of the spread of the predominant strain, ST239. Among MRSA isolates with a vancomycin MIC of 2 mg/L, none of the ST59 isolates was found. Table 2 summarizes the relationship between vancomycin MICs and specific STs.

Table 2 Relationship between specific STs and vancomycin MICs

ST	Range of vancomycin MICs		
	0.5 mg/L ($N = 29$)[a]	1 mg/L ($N = 360$)[b]	2 mg/L ($N = 81$)[c]
ST239, $n = 250$ (%)	2 (6.9)	175 (48.6)	73 (90.1)
ST59, $n = 109$ (%)	19 (65.5)	90 (25)	0
ST5, $n = 74$ (%)	3 (10.3)	65 (18.1)	6 (7.4)

[a] Among 29 isolates, other STs belonged to ST1 (1 isolate), ST45 (3 isolates), and ST537 (1 isolate).
[b] Among 360 isolates, other STs belonged to ST1 (3 isolates), ST8 (3 isolates), ST30 (5 isolates), ST45 (5 isolates), ST78 (1 isolate), ST88 (1 isolate), ST537 (1 isolate), ST573 (8 isolates), and ST900 (3 isolates).
[c] Among 81 isolates, other STs belonged to ST8 (1 isolate) and ST41 (1 isolate).
MIC = minimum inhibitory concentration; ST = sequence type.

Relationship between vancomycin MICs and susceptibilities to linezolid, tigecycline, and daptomycin

All 470 isolates were susceptible to linezolid and tigecycline (MIC range, 0.25—4 mg/L and 0.0125—0.5 mg/L, respectively). Also, all but two isolates were susceptible to daptomycin (MIC range, 0.125—4 mg/L). The susceptibility rate to daptomycin was 99.6%. Among the 81 MRSA isolates with a vancomycin MIC of 2 mg/L, all remained susceptible to linezolid and tigecycline. Moreover, the susceptibility rate of the isolates to daptomycin with a vancomycin MIC of 2 mg/L was 98.8% (MIC range, 0.25—4 mg/L). Table 3 shows the relationship between vancomycin MICs and susceptibilities to linezolid, tigecycline, and daptomycin of these 470 MRSA isolates.

Discussion

Based on our results, four important findings were disclosed. First, according to molecular epidemiology, ST239 (53.2%), ST59 (23.2%), and ST5 (15.7%) remained prevalent among the MRSA blood isolates in our MRSA bacteremia patients from January 2006 to December 2008, accounting for 92.1% of all MRSA blood isolates. Second, the proportion of ST239 isolates decreased significantly statistically. Third, the proportion of ST59 isolates increased, although the change was not statistically significant. However, the proportion of MRSA isolate belonging to ST59 among all HA-MRSA isolates increased significantly. The likelihood of ST59 replacing ST239 and then becoming the predominant strain among all MRSA blood isolates deserves further epidemiological studies in the future. Fourth, 17.2% of 470 MRSA blood isolates expressed a high MIC level (2 mg/L) of vancomycin. MRSA blood isolates having a high MIC (2 mg/L) of vancomycin in this study may be because of the spread of the predominant strain, ST239. Moreover, linezolid, tigecycline, and daptomycin remained highly active *in vitro* against these MRSA blood isolates, even those with a vancomycin MIC of 2 mg/L.2

CA-MRSA preferred to carry fewer antimicrobial resistance genes, compared with HA-MRSA.[21] Closely examining

Table 3 Relationship between vancomycin MICs and susceptibilities to linezolid, tigecycline, and daptomycin

Vancomycin MICs (mg/L)	Range of MICs (susceptible, %)		
	Linezolid (mg/L)	Tigecycline (mg/L)	Daptomycin (mg/L)
0.5 ($N = 29$, 6.2%)	1—4 (100)	0.032—0.25 (100)	0.25—0.5 (100)
1 ($N = 360$, 76.6%)	0.25—4 (100)	0.0125—0.5 (100)	0.125—2[a] (99.7)
2 ($N = 81$, 17.2%)	0.25—4 (100)	0.032—0.5 (100)	0.25—4[b] (98.8)

[a] One isolate was nonsusceptible to daptomycin (MIC = 2 mg/L).
[b] One isolate was nonsusceptible to daptomycin (MIC = 4 mg/L).
MIC = minimum inhibitory concentration.

how vancomycin MICs and STs of MRSA are related revealed that most (65.5%) of the MRSA isolates with a vancomycin MIC of 0.5 mg/L belonged to ST59, whereas ST239 isolates constituted most (90.1%) of the MRSA isolates with a vancomycin MIC of 2 mg/L. None of the ST59 isolates had a high MIC (2 mg/L) of vancomycin. The likelihood that ST59 isolates become isolates with high vancomycin MICs in the future, while responding to the selection pressure of current antimicrobial agents in a hospital, requires continuous surveillance.

Chen et al.[6] indicated that ST239-SCC*mec* III (70.8%), ST59-SCC*mec* IV/V (18.7%), and ST5-SCC*mec* II (4.7%) accounted for most of the 257 MRSA bloodstream isolates in our hospital from 1995 to 2006. Although ST239 isolates prevailed over the previous 12-year period, the proportion declined from more than 90% to 48%. Furthermore, the proportion of ST59 and ST5 isolates increased concurrently. Our study results reflected their finding that the proportion of ST239 clones significantly decreased during the study period. However, although ST59 clones increased during the same period, the changes were not statistically significant. The likelihood of ST59 strain replacing the traditional HA-MRSA strain, ST239, to become the predominant strain causing health care—associated infections in the future warrants further investigation.

Linezolid, tigecycline, and daptomycin may be the therapeutic alternatives among patients with MRSA bacteremia caused by an MRSA isolate with a vancomycin MIC greater than or equal to 1.5—2 mg/L if based on just the *in vitro* susceptibility test results.[12,13] However, on the basis of pharmacodynamic studies, tigecycline is not suitable to treat MRSA bacteremia for its low serum level and bacteriostatic property.[12] In addition, although some studies showed that linezolid might not be inferior to vancomycin in treating the outcomes of *S aureus* bacteremia, linezolid also belongs to bacteriostatic agents.[22] Therefore, only daptomycin has been approved to treat *S aureus* bacteremia by the U.S. Food and Drug Administration among the three drugs till date.[12,13] In this study, nearly all MRSA blood isolates, even with a vancomycin MIC of 2 mg/L, remained highly susceptible to daptomycin, except for only two isolates (MIC = 2 mg/L and 4 mg/L). The result indicated that daptomycin might be an optimal therapeutic alternative to treat bacteremia caused by MRSA isolates, even with a vancomycin MIC of 2 mg/L.

Despite its contributions, this study has certain limitations. First, the study period is not sufficiently long to observe a definite secular change; hence, continuous surveillance is required to analyze the trend of molecular epidemiology. Second, MRSA blood isolates were collected from a single hospital. Interhospital differences may arise concerning patients' characteristics and antibiotic usage, making the results inapplicable to other institutions.

In conclusion, our study demonstrated that the proportion of MRSA isolates with a vancomycin MIC of 2 mg/L was 17.2% among MRSA blood isolates collected from adult patients during January 2006 to December 2008. A significant proportion of MRSA blood isolates with high MICs (2 mg/L) of vancomycin may be attributable to the spread of the predominant strain, ST239. Additionally, ST239 remained the predominant strain during the 3-year period but with a significant trend to decrease. Linezolid, tigecycline, and daptomycin remained highly active against MRSA blood isolates, even though an MRSA isolate had a vancomycin MIC of 2 mg/L. However, MRSA blood isolates require to be monitored continuously to further analyze the fluctuating molecular epidemiology and relationship between vancomycin MICs and specific STs.

References

1. Ho M, McDonald LC, Lauderdale TL, Yeh LL, Chen PC, Shiau YR. Surveillance of antibiotic resistance in Taiwan, 1998. *J Microbiol Immunol Infect* 1999;**32**:239—49.
2. Chamis AL, Peterson GE, Cabell CH, Corey GR, Sorrentino RA, Greenfield RA, et al. *Staphylococcus aureus* bacteremia in patients with permanent pacemakers or implantable cardioverter-defibrillators. *Circulation* 2001;**104**:1029—33.
3. Salmenlinna S, Lyytikinen O, Kotilainen P, Scotford R, Siren E, Vuopio-Varkila J. Molecular epidemiology of methicillin-resistant *Staphylococcus aureus* in Finland. *Eur J Clin Microbiol Infect Dis* 2000;**19**:101—7.
4. Wang JT, Chen YC, Yang TL, Chang SC. Molecular epidemiology and antimicrobial susceptibility of methicillin-resistant *Staphylococcus aureus* in Taiwan. *Diagn Microbiol Infect Dis* 2002;**42**:199—203.
5. Wang JT, Fang CT, Chen YC, Wu CL, Chen ML, Chang SC. Staphylococcal cassette chromosome *mec* in MRSA, Taiwan. *Emerg Infect Dis* 2007;**13**:494—7.
6. Chen CJ, Hsueh PR, Su LH, Chiu CH, Lin TY, Huang YC. Change in the molecular epidemiology of methicillin-resistant *Staphylococcus aureus* bloodstream infections in Taiwan. *Diagn Microbiol Infect Dis* 2009;**65**:199—201.
7. D'Agata EM, Webb GF, Horn MA, Moellering Jr RC, Ruan S. Modeling the invasion of community-acquired methicillin-resistant *Staphylococcus aureus* into hospitals. *Clin Infect Dis* 2009;**48**:274—84.

8. Davis SL, Rybak MJ, Amjad M, Kaatz GW, McKinnon PS. Characteristics of patients with healthcare-associated infection due to SCC *mec* type IV methicillin-resistant *Staphylococcus aureus*. *Infect Control Hosp Epidemiol* 2006;**27**:1025—31.
9. Popovich KJ, Weinstein RA, Hota B. Are community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) strains replacing traditional nosocomial MRSA strains? *Clin Infect Dis* 2008;**46**:795—8.
10. Lodise TP, Graves J, Evans A, Graffunder E, Helmecke M, Lomaestro BM, et al. Relationship between vancomycin MIC and failure among patients with MRSA bacteremia treated with vancomycin. *Antimicrob Agents Chemother* 2008;**52**:3315—20.
11. Hidayat LK, Hsu DI, Quist R, Shriner KA, Wong-Beringer A. High-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* infections: efficacy and toxicity. *Arch Intern Med* 2006;**166**:2138—44.
12. Micek ST. Alternatives to vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* infections. *Clin Infect Dis* 2007;**45**:S184—90.
13. Drees M, Boucher H. New agents for *Staphylococcus aureus* endocarditis. *Curr Opin Infect Dis* 2006;**19**:544—50.
14. Naimi TS, LeDell KH, Como-Sabetti K, Borchardt SM, Boxrud DJ, Etienne J, et al. Comparison of community- and health care-associated methicillin-resistant *Staphylococcus aureus* infection. *JAMA* 2003;**290**:2976—84.
15. Seybold U, Kourbatova EV, Johnson JG, Halvosa SJ, Wang YF, King MD, et al. Emergence of community-associated methicillin-resistant *Staphylococcus aureus* USA300 genotype as a major cause of health care-associated blood stream infection. *Clin Infect Dis* 2006;**42**:647—56.
16. Wang JL, Wang JT, Chen SY, Hsueh PR, Kung HC, Chen YC, et al. Adult methicillin-resistant *Staphylococus aureus* bacteremia in Taiwan: clinical significance of non-multi-resistant antibiogram and Panton-Valentine leukocidin gene. *Diagn Microbiol Infect Dis* 2007;**59**:365—71.
17. *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard-seventh edition, M7-A7*. Wayne, PA: Clinical and Laboratory Standards Institute; 2006.
18. *Performance standards for antimicrobial susceptibility testing. Nineteenth informational supplement, M100-S19*. Wayne, PA: Clinical and Laboratory Standards Institute; 2009.
19. The European Committee for Antimicrobial Susceptibility Testing (EUCAST) Steering Committee. EUCAST technical note on tigecycline. *Clin Microbiol Infect* 2006;**12**:1147—9.
20. Enright MC, Day NP, Davies CE, Peacock SJ, Spratt BG. Multilocus sequence typing for characterization of methicillin-resistant and methicillin-susceptible clones of *Staphylococcus aureus*. *J Clin Microbiol* 2002;**38**:1008—15.
21. Baba T, Takeuchi F, Kuroda M, Yuzawa H, Aoki K, Oguchi A, et al. Genome and virulence determinants of high virulence community-acquired MRSA. *Lancet* 2002;**359**:1819—27.
22. Shorr AF, Kunkel MJ, Kollef M. Linezolid versus vancomycin for *Staphylococcus aureus* bacteraemia: pooled analysis of randomized studies. *J Antimicrob Chemother* 2005;**56**: 923—9.