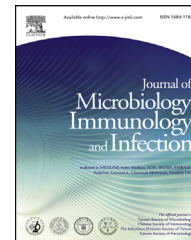




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ORIGINAL ARTICLE

Relationship of teicoplanin MICs to treatment failure in teicoplanin-treated patients with methicillin-resistant *Staphylococcus aureus* pneumonia

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Received 9 April 2012; received in revised form 14 June 2012; accepted 28 June 2012

KEYWORDS

MRSA;
Pneumonia;
Teicoplanin

Background/Purpose: The objective of this study was to determine the predictive value of teicoplanin minimal inhibitory concentrations (MICs) for treatment failure among patients with methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia.

Methods: In this study, all patients with ≥ 1 tracheal aspirates or sputum cultures positive for MRSA admitted to the hospital between April 2011 and September 2011 were reviewed. We enrolled patients who are ≥ 18 years of age, with a diagnosis of pneumonia, and with a receipt of teicoplanin therapy throughout the course. The relationship between teicoplanin Etest MICs and treatment outcomes of MRSA pneumonia was analyzed to identify the breakpoint of teicoplanin MICs influencing treatment outcomes.

Results: Of the 80 patients enrolled, 31 had a lower teicoplanin MIC level (< 2.0 mg/L) and 49 had a higher MIC level (≥ 2.0 mg/L) for MRSA. The lower MIC group had a higher clinical resolution rate in 14 days [24 (77.4%) vs. 23 (46.9%), $p = 0.007$] and a lower treatment failure rate at the end of teicoplanin treatment [4 (12.9%) vs. 18 (36.7%), $p = 0.020$]. A comparison between the treatment success and failure groups showed that the former had a longer duration of teicoplanin use (18.76 ± 10.34 vs. 12.41 ± 5.65 days; $p = 0.014$). Results of a multivariate analysis showed that teicoplanin MICs ≥ 2.0 mg/L and shorter duration of teicoplanin therapy were independent risk factors for treatment failure.

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Conclusion: A higher teicoplanin MIC value (≥ 2.0 mg/L) may predict the treatment failure among patients with teicoplanin-treated MRSA pneumonia.

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Introduction

Staphylococcus aureus has been increasingly recognized as an important pathogen of health care-associated pneumonia (HCAP), hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and community-acquired pneumonia (CAP).¹ Previous reports have shown that infections due to methicillin-resistant *S. aureus* (MRSA) strains had a worse prognosis than that caused by methicillin-susceptible *S. aureus* (MSSA) strains.^{2,3} Few studies have even stated that the possible excess mortality is related to MRSA stains in patients who had nosocomial pneumonia.^{2–5}

Vancomycin has been the standard drug for the treatment of serious MRSA infections since the early 1980s, when MRSA infection became significant in the hospital setting.⁶ However, several studies reported that the activity of vancomycin for the treatment of VAP due to *S. aureus* was probably suboptimal.⁷ Meanwhile, vancomycin was reported to have a poor penetration in the lungs,⁸ and was an independent risk factor of hospital death in patients with adequately treated bacteremic pneumonia.³ Furthermore, a study regarding the relationship between vancomycin minimum inhibitory concentrations (MICs) and mortality in patients with MRSA, HAP, VAP, or HCAP infections showed that vancomycin therapy for pneumonia caused by MRSA with an MIC value between 1 and 2 mg/L should be cautious, and alternative therapy should be considered.⁹

Teicoplanin is a glycopeptide alternative to vancomycin and has been widely used for the treatment of pneumonia caused by MRSA in Europe and Taiwan. In our recent study, we demonstrated that MRSA blood isolates with teicoplanin MIC > 1.5 mg/L could predict a poor outcome and higher mortality among patients with teicoplanin-treated MRSA bacteremia.¹⁰ Following our publication, a doubt was raised regarding the influence of teicoplanin MICs on clinical outcomes in patients with serious MRSA pneumonia infection. We therefore conducted a 6-month retrospective cohort study to examine MRSA respiratory isolates by Etest for identifying the MIC breakpoint of teicoplanin influencing treatment outcomes.

Materials and methods

Settings

Chang Gung Memorial Hospital (CGMH) at Linkou is a 3715-bed tertiary care medical center in Northern Taiwan. This retrospective cohort study has been approved by the Institutional Research Board of CGMH-Linkou (No. 101-0654B).

Study design and identification of patients

Between April 2011 and September 2011, all the tracheal aspirates or sputum cultures positive for MRSA were collected in advance and stored in skimmed milk at -70 °C before the study began. Using the computer-assisted records of the Clinical Microbiology Laboratory, we searched for the hospitalized patients who are ≥ 18 years of age and whose tracheal aspirates or sputum cultures were positive for MRSA.

Pneumonia was diagnosed according to the recommendation by the American Thoracic Society (ATS) and Infectious Diseases Society of America.¹¹ In brief, pneumonia was defined as the chest radiograph demonstrating new or progressive infiltrates, as well as at least two of the following clinical signs¹²: fever (≥ 38 °C) or hypothermia (< 35.5 °C), abnormal white blood cell count ($> 12,000$ cells/mm³ or < 4000 cells/mm³), oxygen desaturation, and increasing amount of purulent sputum. MRSA pneumonia was defined as clinical presence of pneumonia accompanied with a tracheal aspirate or sputum culture positive for MRSA from 1 week before to 3 days after the first dose of teicoplanin therapy. Only the first episode of MRSA pneumonia was reviewed. Tracheal aspirates and sputum specimens qualified for performing cultures should have > 25 neutrophils and < 10 epithelial cells per low-power field on Gram staining. Culture growth was semi quantitative based on the degree of growth or number of colonies in the primary, secondary, and tertiary streaking zones on an agar plate.

Patients were excluded if one of the following criteria was met: age < 18 years, receipt of teicoplanin treatment ≤ 3 days, presence of MRSA airway colonization, clinical pulmonary infection score (CPIS)¹³ < 6 , coexisting MRSA bacteremia, or MRSA endovascular lesions with or without septic emboli before pneumonia.

Patients with MRSA pneumonia were identified and their medical records were reviewed before teicoplanin MIC data were available. The clinical data for analysis included demographics, comorbidities, laboratory data, disease severity, and treatment outcomes. Patients were evaluated for the relationship between teicoplanin MICs and treatment outcomes if they had no teicoplanin allergy and received teicoplanin therapy with an adequate dosage throughout the treatment course. The adequate dosage of teicoplanin administered was based on the manufacturer's instruction (Sanofi-Aventis, Taiwan): a loading dose of 6 mg/kg (maximum 400 mg per dose) for 3 doses 12 hours apart and then every 24 hours, adjusted by the patient's renal function.

Demography and comorbidity

We categorized the enrolled patient into CAP, HAP, VAP, and HCAP. HAP was defined as the occurrence of pneumonia

after over 48 hours of hospitalization.^{14,15} VAP was considered if pneumonia developed more than 48 hours after endotracheal intubation.^{14,16} HCAP was diagnosed on the basis of the presence of any one of the following risk factors: hospitalization in an acute care hospital for 2 days or more in the preceding 90 days; residence of a nursing home or extended care facility; chronic dialysis within 30 days; receipt of recent intravenous antibiotics, chemotherapy, or wound care within the past 30 days.^{14,17,18} Demographic data included gender and age. Comorbidities included hypertension, diabetes mellitus, heart failure, chronic lung diseases such as chronic obstructive pulmonary disease (COPD) or old pulmonary tuberculosis, renal insufficiency with or without requirement of dialysis, malignancies, and cerebrovascular accident. Data on fraction of inspired oxygen (FiO₂) supplement, partial pressure of oxygen (PaO₂) in arterial blood, and the white blood cell counts within 24 hours before or after the first dose of teicoplanin were gathered by reviewing the in-patient medical records.

Clinical conditions and efficacy assessment

We used sequential organ failure assessment (SOFA) score systems¹⁹ with the available clinical, laboratory, image, and microbiological data on each enrolled patient at the beginning of teicoplanin therapy. Findings of chest radiographs, follow-up sputum culture results, and vital signs during hospitalization were recorded. Follow-up microbial results were not available from some patients and those were considered as missing data in the statistical analysis. Clinical resolution of pneumonia in 14 days was defined as (1) improvement on the follow-up chest radiographs, or (2) survival with stationary findings on chest radiographs and defervescence, decreased sputum amount, or respiratory rate less than 20 times per minute by medical records. Defervescence was defined as afebrile status for at least 3 days. Treatment failure at the end of teicoplanin treatment was considered if there was deterioration of the follow-up chest radiographs with persistent MRSA-positive sputum cultures or no clinical improvement, including fever (≥ 38 °C) or hypothermia (< 35.5 °C), shock status (mean arterial pressure ≤ 70 mmHg), increasing amount of purulent sputum, respiratory rate ≥ 20 times per minute, or relapse of MRSA-positive cultures. Eradication refers to no isolation of MRSA from the follow-up cultures done before and 7 days after cessation of teicoplanin therapy.

Laboratory methods

S. aureus was identified according to the following findings: aerobic, Gram-positive cocci in clusters on a Gram's stain and a catalase-positive, coagulase-positive, and ornithine-negative reaction.²⁰ MRSA was identified by the detection of oxacillin resistance with a 30- μ g cefoxitin disk and Mueller–Hinton agar according to the Clinical and Laboratory Standards Institute recommendations.²¹ All the MRSA respiratory isolates collected from the enrolled patients were preserved in skimmed milk at -70 °C until they were further tested. Teicoplanin MICs were determined using Etest teicoplanin strips (AB BIODISK, Solna, Sweden) with an inoculum

equivalent to 0.5 McFarland turbidity, brain–heart infusion agar (Oxoid, Basingstoke, UK), and incubation for 48 hours at 35–37 °C. The quality control strain was MSSA ATCC 29213. The MIC breakpoint for teicoplanin resistance is > 2 mg/L in accordance with the European Committee on Antimicrobial Susceptibility testing (EUCAST).²²

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (version 19; IBM Corporation, Somers, New York, USA). Descriptive statistics were used to summarize the continuous variables, including the number of observations, mean, and standard deviation. Student *t* test or Wilcoxon test was considered for the test statistics, depending on the validity of the normality assumption. Chi-square test or Fisher's exact test was used to test the categorical variables. Odds ratios (ORs) and 95% confidence interval (CI) were calculated. Variables with $p < 0.2$ in univariate analysis were included in a logistic regression model for multivariate analysis. All tests were two-tailed, and $p < 0.05$ was considered significant in multivariate analysis.

Results

A total of 91 patients diagnosed with MRSA pneumonia were identified initially. Of them, 11 patients were excluded according to the aforementioned exclusion criteria. Therefore, 80 patients with teicoplanin-treated MRSA pneumonia were enrolled in this study with a mean age of 74.8 years with male predominance (81.3%). As for disease severity, SOFA score was 6.5. The major comorbidities were hypertension (57.5%) and diabetes mellitus (40%). Twenty-five patients (31.3%) had chronic lung diseases, including COPD (14, 17.5%) and old pulmonary tuberculosis (11, 13.8%). Thirty-four patients (42.5%) had polymicrobial pulmonary infections and the mean duration of teicoplanin use was 17.01 days.

Of these 80 patients, 31 had MRSA isolates with teicoplanin MICs < 2.0 mg/L and 49 had those isolates with teicoplanin MICs ≥ 2.0 mg/L. They were divided into the lower MIC (< 2.0 mg/L) and higher MIC (≥ 2.0 mg/L) groups. The comparison of their demographics, comorbidities, laboratory data, disease severity, and treatment outcomes is summarized in Table 1. There was no significant difference between these two groups with respect to the demographics, comorbidities, lab data, disease severity, crude mortality, and microbial eradication. Compared with the higher MIC group, the lower MIC group had a higher clinical resolution rate in 14 days [24 (77.4%) vs. 23 (46.9%); $p = 0.007$] and a lower treatment failure rate at the endpoint of teicoplanin therapy [4 (12.9%) vs. 18 (36.7%); $p = 0.020$].

To identify risk factors for treatment failure at the endpoint of teicoplanin therapy, these 80 patients were divided into the treatment success and treatment failure groups (Table 2). There were no statistical differences between these two groups in age, gender, source of pneumonia, underlying diseases, and initial disease severity while MRSA pneumonia was diagnosed. Compared with the failure group, patients with treatment success had a longer

Table 1 Comparison of clinical characteristics of patients with methicillin-resistant *Staphylococcus aureus* pneumonia between the groups of teicoplanin MICs < 2.0 mg/L and ≥ 2.0 mg/L

Variables	MIC < 2.0 mg/L (n = 31)	MIC ≥ 2.0 mg/L (n = 49)	p
Demographics			
Gender (male)	26 (83.9)	39 (79.6)	0.633
Age (year)	76.15 ± 12.81	73.94 ± 15.92	0.517
Community-acquired pneumonia	5 (16.1)	8 (16.3)	0.981
Hospital-acquired pneumonia	26 (83.9)	41 (83.7)	0.981
Ventilator-associated pneumonia	12 (38.7)	15 (30.6)	0.456
Health care-associated pneumonia	5 (16.1)	5 (10.2)	0.498
Comorbidities			
Hypertension	20 (64.5)	26 (53.1)	0.313
Diabetes mellitus	13 (41.9)	19 (38.8)	0.779
Congestive heart failure	9 (29.0)	7 (14.3)	0.108
Chronic obstructive pulmonary disease	3 (9.7)	11 (22.4)	0.143
Old pulmonary tuberculosis	5 (16.1)	6 (12.2)	0.742
Chronic renal failure without dialysis	9 (29.0)	11 (22.4)	0.508
End-stage renal disease	5 (16.1)	6 (12.2)	0.742
Malignancies	7 (22.6)	14 (28.6)	0.553
Cerebrovascular accident	11 (35.5)	18 (36.7)	0.910
Laboratory data			
FiO ₂	51.13 ± 24.66	42.14 ± 17.26	0.082
PaO ₂	109.70 ± 55.67	91.15 ± 36.67	0.107
Creatinine (mg/dL)	1.83 ± 2.15	2.08 ± 2.07	0.605
White blood cell count (cells/mm ³)	15,803.23 ± 8209.69	14,987.76 ± 6643.31	0.627
Disease severity			
SOFA score	6.65 ± 2.89	6.41 ± 3.53	0.755
Stay in intensive care unit (ICU)	18 (58.1)	27 (55.1)	0.795
Treatment outcome			
Treatment duration (days)	16.74 ± 8.69	17.16 ± 10.37	0.851
Clinical resolution in 14 days	24 (77.4)	23 (46.9)	0.007
Clinical resolution in 28 days	21 (67.7)	26 (53.1)	0.194
Treatment failure	4 (12.9)	18 (36.7)	0.020
Crude mortality	14 (45.2)	24 (49.0)	0.739
Mortality before 14 th day	5 (16.1)	5 (10.2)	0.498
Mortality before 28 th day	9 (29.0)	17 (34.7)	0.598
Microbial eradication ^a	13/22 (59.1)	13/30 (43.3)	0.262

^a Microbial eradication: only 52 patients had subsequent follow-up respiratory tract cultures, 22 in the low MIC group, and 30 in the higher MIC group.

Categorical data are the number (%) of subjects, and continuous data are expressed as mean ± standard deviation.

MIC = minimal inhibitory concentration; FiO₂ = fraction of inspired oxygen; PaO₂ = partial pressure of oxygen in arterial blood; SOFA = sequential organ failure assessment.

duration of teicoplanin use (18.76 ± 10.34 vs. 12.41 ± 5.65 days; $p = 0.014$). Multivariate analysis showed that the teicoplanin MIC ≥ 2.0 mg/L (adjusted OR, 4.58; 95% CI: 1.261–16.646) and treatment duration (adjusted OR, 0.89; 95% CI: 0.822–0.971) were independent risk factors for treatment failure at the endpoint of teicoplanin therapy (Table 3). The survival analysis for MRSA pneumonia with teicoplanin MIC < 2 mg/L and ≥ 2.0 mg/L ($p = 0.201$) is presented in Fig. 1.

Microbiological outcome

In our study, only 52 patients had subsequent follow-up respiratory tract cultures available for evaluation of

microbiological outcomes. Among them, the lower MIC group had a better eradication rate of MRSA (13/22, 59.1%) than the higher one (13/30, 43.3%) (Table 1). However, there was no significant difference between them.

Discussion

A systematic review in 1999 revealed that inadequate antimicrobial treatment of patients requiring intensive care unit (ICU) admission was an important determinant of hospital mortality.²³ Inadequate antimicrobial treatment included the absence of antimicrobial agents for a specific class of microorganisms and the administration of an antimicrobial agent which was not active *in vitro* against the

Table 2 Univariate analysis of risk factors for treatment failure

Variables	Treatment success (n = 58)	Treatment failure (n = 22)	p
Demographic			
Gender (male)	48 (82.8)	17 (77.3)	0.749
Age (year)	76.27 ± 14.01	70.91 ± 16.23	0.180
Community-acquired pneumonia	8 (13.8)	5 (22.7)	0.331
Hospital-acquired pneumonia	50 (86.2)	17 (77.3)	0.331
Comorbidities			
Hypertension	37 (63.8)	9 (40.9)	0.683
Diabetes mellitus	24 (41.4)	8 (36.4)	0.683
Congestive heart failure	11 (19.0)	5 (22.7)	0.733
Chronic obstructive pulmonary disease	11 (19.0)	3 (13.6)	0.747
Old pulmonary tuberculosis	7 (12.1)	4 (18.2)	0.483
Chronic renal failure without dialysis	13 (22.4)	7 (31.8)	0.386
End-stage renal disease	9 (15.5)	2 (9.1)	0.718
Malignancies	13 (22.4)	8 (36.4)	0.205
Cerebrovascular accident	22 (37.9)	7 (31.8)	0.612
Laboratory data			
FiO ₂	44.91 ± 20.53	47.50 ± 21.75	0.622
PaO ₂	99.96 ± 43.51	94.05 ± 51.44	0.607
Creatinine (mg/dL)	1.95 ± 2.10	2.07 ± 2.09	0.818
White blood cell count (cells/mm ³)	15,358.62 ± 7693.38	15,159.09 ± 6089.23	0.913
Disease severity			
SOFA score	6.33 ± 3.32	6.95 ± 3.21	0.449
Stay in intensive care unit (ICU)	32 (55.2)	13 (59.1)	0.752
Treatment			
Treatment duration (days)	18.76 ± 10.34	12.41 ± 5.65	0.014

Categorical data are the number (%) of subject, and continuous data are expressed as mean ± standard deviation.

FiO₂ = fraction of inspired oxygen; PaO₂ = partial pressure of oxygen in arterial blood; SOFA = sequential organ failure assessment.

pathogens. Treatment failure due to inadequate teicoplanin treatment for MRSA pneumonia was excluded in our study because of the real-time online hospital-wide computerized antimicrobial approval system (HCAAS) at CGMH-Linkou.²⁴ In brief, any antibiotic prescribed by the physicians in our hospital will be reviewed by Infectious Diseases specialists online in time. All the patients' electronic medical records, laboratory data, procedure examination, and image studies are available to check from the HCAAS. This strategy is to monitor whether the prescribed antimicrobial regimens were rational or not.

Table 3 Multivariate analysis of risk factors associated with treatment failure

	OR	95% CI	p
MIC ≥ 2.0 mg/L	4.581	1.261–16.646	0.021
Treatment duration	0.893	0.822–0.971	0.008
Age	0.970	0.935–1.007	0.109

Risk factors with $p < 0.2$ in univariate analysis in Table 2 and the factor of MIC ≥ 2.0 mg/L were considered for inclusion in a multivariate analysis.

CI = confidence interval; MIC = minimum inhibitory concentration; OR = odds ratio.

There were substantial differences in clinical characteristics between the treatment success and failure groups. The unadjusted creatinine levels, oxygen supplement, and disease severity scoring systems such as SOFA score, CPIS, and ICU admission rate were higher in the treatment failure group although there were no statistical differences in the univariate analysis. As reported previously, MRSA infection was more common among patients with worse severity scores, infections in ICU, or MRSA carriage.⁵

Several studies have demonstrated the relationship between glycopeptide MICs and treatment failure in patients with MRSA infections. A study conducted by Charlesworth et al showed that a higher teicoplanin MIC, as found by Etest or agar incorporation, was associated with a lower survival rate in critically ill patients.²⁵ A couple of other studies reported that a vancomycin MIC value > 1.5 mg/L was associated with a higher rate of treatment failure and a higher 30-day mortality.^{26,27} In a recent study by Chang et al, a higher teicoplanin MIC value (>1.5 mg/L) may be associated with unfavorable outcomes and higher mortality among patients with teicoplanin-treated MRSA bacteremia.¹⁰ Thus, we focused on patients with MRSA pneumonia and chose the teicoplanin MIC value of 2.0 mg/L as the cutoff value. This study revealed that a lower teicoplanin MIC value (<2.0 mg/L) for MRSA was associated with a higher clinical resolution rate in 14 days

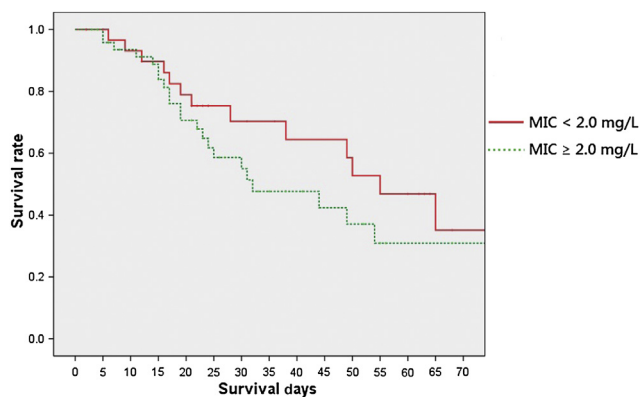


Figure 1. Survival analysis of patients with pneumonia caused by methicillin-resistant *Staphylococcus aureus* with teicoplanin minimum inhibitory concentrations (MICs) < 2.0 mg/L and \geq 2.0 mg/L ($p = 0.201$).

and a lower treatment failure rate among patients with teicoplanin-treated MRSA pneumonia. Multivariate analysis showed that higher teicoplanin MIC value (≥ 2.0 mg/L) and shorter teicoplanin treatment duration were independent risk factors for treatment failure at the endpoint. This result was similar to the findings of Haque et al, who described that the mortality of patients with MRSA pneumonia treated with vancomycin would increase with elevated vancomycin MIC values.⁹ The MRSA eradication rate in respiratory tract was low in this study, but the microbial eradication was not significantly associated with clinical outcomes.

There were some limitations in our study. First, there were some patients with incomplete follow-up data for sputum cultures because all the airway cultures were requested by clinicians based on their discretion. Second, no molecular analysis for epidemiological survey was performed to identify the specific MRSA strains. MRSA strains with specific resistant genes could influence MIC values.^{28,29} Besides, some experts recommended that a higher loading dose of teicoplanin (e.g., 12 mg/kg) may correlate with a better outcome or a higher serum level.³⁰ However, there was no case undertaken with such a dose in our study. Finally, many patients had polymicrobial isolates from airway cultures and received other broad-spectrum antibiotic therapy while receiving teicoplanin. These combination therapeutic regimens may impact the efficacy of teicoplanin therapy.

In conclusion, our study affords preliminary evidence that the teicoplanin Etest MIC cutoff value of 2.0 mg/L could be a predictive value for clinical outcomes among patients with teicoplanin-treated MRSA pneumonia, and even the teicoplanin MICs for MRSA isolates are still within the susceptible breakpoint according to EUCAST criteria in 2011. The independent risk factors for treatment failure were higher teicoplanin MIC value (≥ 2.0 mg/L) for MRSA and shorter duration of teicoplanin therapy. The assessment of the changes of teicoplanin MIC values should be taken into consideration, especially among patients who underwent teicoplanin treatment without clinical resolution. Other alternative therapies should be seriously considered for the MRSA isolates with teicoplanin MICs ≥ 2.0 mg/dL.

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