Intensive Care Med (2011) 37:639–647
DOI 10.1007/s00134-011-2130-7

ORIGINAL

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Relationship between the MIC of vancomycin and clinical outcome in patients with MRSA nosocomial pneumonia

Received: 30 June 2010
Accepted: 1 September 2010
Published online: 21 January 2011

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Abstract *Purpose:* The objective of this study is to assess the distribution of vancomycin minimum inhibitory concentrations (MICs) in methicillin-resistant *Staphylococcus aureus* (MRSA) isolates and evaluate the efficacy of vancomycin relative to vancomycin MICs in adult patients with MRSA nosocomial pneumonia. *Methods:* This retrospective cohort study involved adults with MRSA nosocomial pneumonia treated with vancomycin. Vancomycin MICs were determined using Etest. Patients with MRSA and vancomycin MICs >1.5 μg/mL and those with MRSA and MICs ≤1 μg/mL were placed in the high- and low-MIC group, respectively. The primary outcomes assessed were clinical response and relapse of MRSA pneumonia within 28 days after vancomycin discontinuation. Secondary outcomes included 28-day mortality, in-hospital mortality and length of hospital stay. *Results:* Seventy patients met the inclusion criteria. Mean age and mean Acute Physiological and Chronic Health Evaluation (APACHE) II score upon intensive care unit (ICU) admission of these patients were 67.0 years and 25.9, respectively. Thirty-four (48.6%) isolates had high vancomycin MICs, and 36 (51.4%) had low MICs. There were no significant differences in baseline characteristics between the two groups. Early clinical response rates in the low- and high-MIC groups were 63.9% and 35.3%, respectively ($p = 0.031$). The high-MIC group had an 8% lower final clinical response rate, but this difference was not significant ($p = 0.609$). The relapse rate within 28 days was significantly higher in the high-MIC group than in the low-MIC group (29.6% versus 6.9%, $p = 0.038$). On multivariate analysis, infection by high-MIC strains was an independent predictor of early clinical response failure. *Conclusions:* About half of the MRSA isolates had high vancomycin MIC. Patients infected with these strains showed slower clinical response and higher relapse rate than patients infected with low vancomycin MIC isolates.

Keywords Vancomycin minimum inhibitory concentration (MIC) · Methicillin-resistant *Staphylococcus aureus* (MRSA) · Nosocomial pneumonia

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major pathogen of nosocomial pneumonia [1–3]. Despite early and appropriate therapy, this type of pneumonia is associated with high mortality rates and healthcare costs [4, 5]. Although vancomycin has been the mainstay for treatment of MRSA infections, the drug may not be adequate for patients with MRSA pneumonia [6, 7]. The unsatisfactory results observed in patients treated with vancomycin may be attributed to the relatively large size of the vancomycin molecule, which reduces the drug's ability to penetrate into the alveolar lining fluid (ALF) and alveolar macrophages [8, 9]. As a result, the concentration of vancomycin in ALF is only one-sixth that in plasma, reducing drug efficacy in patients with MRSA pneumonia. The limited efficacy of vancomycin may also be associated with diminished bactericidal activity against MRSA strains with higher, although still susceptible, vancomycin minimal inhibitory concentrations (MICs) (>1 μg/mL). Indeed, an increase in vancomycin MIC from 1 to 2 μg/mL, which remains in the "susceptible" range, has been independently associated with treatment failure in MRSA infections treated with vancomycin [10–14], indicating a correlation between vancomycin MIC and treatment outcomes after such infections.

A recent study of 662 MRSA strains isolated over a 5-year period showed that the geometric mean MIC increased significantly over time, from 0.62 (range 0.25–1 μg/mL) to 0.94 μg/mL (range 0.5–2 μg/mL) ($p < 0.001$) [15]. This phenomenon, called vancomycin minimum inhibitory concentration creep (MIC creep), is of clinical concern because poorer treatment outcomes have been associated with higher vancomycin MICs.

Most previous studies have focussed on patients with MRSA bacteraemia rather than those with MRSA pneumonia. Therefore, little is known about the relationship between vancomycin MIC and clinical outcomes, including relapse, in patients with MRSA nosocomial pneumonia. We therefore assessed the distribution of vancomycin MICs in MRSA isolates and evaluated vancomycin efficacy relative to vancomycin MIC in adult patients with MRSA nosocomial pneumonia.

Materials and methods

Study design and population

This retrospective cohort study involved patients treated for MRSA nosocomial pneumonia at the Asan Medical Center (AMC), a 2,800-bed referral hospital in Seoul, Korea, from 1 October 2008 to 31 December 2009. The study was approved by the hospital's Institutional Review Board; informed consent was not required because this was not an interventional study.

Patients were included if they (1) were 18 years of age or older; (2) were diagnosed with nosocomial pneumonia, defined as pneumonia acquired in a skilled nursing facility or 48 h or more after hospital admission; and (3) had been treated with vancomycin for 48 h or more. Patients were required to have clinical features compatible with pneumonia, with one or more of the following signs and symptoms: production of purulent sputum or a worsening in sputum character; fever or hypothermia (oral temperature ≥38°C or ≤35.5°C); systolic blood pressure (BP) <90 mmHg; and/or total leucocyte count >10,000/μL, leucopoenia (total leucocyte count <4,500/μL), or >15% immature neutrophils regardless of total leucocyte count. Chest radiographs of all patients had to be consistent with a diagnosis of pneumonia (e.g., new or progressive infiltrates or consolidation, with/without pleural effusion). If a patient had more than one episode during the study period, only the first episode was considered. For patients from whom multiple MRSA cultures were grown, the vancomycin MIC of only the index isolate was considered in the analysis.

Exclusion criteria included: clinical pulmonary infection score (CPIS) value <6; hypersensitivity to vancomycin; co-infection with Gram-positive organisms known to be resistant to vancomycin; treatment for <48 h; pregnancy; presence of meningitis, endocarditis or osteomyelitis; CD4 cell count <200/mm^3 secondary to human immunodeficiency virus infection; or severe neutropaenia (<500/mm^3).

Data collection

Data were gathered from medical records using a structured form. The demographic and clinical characteristics recorded were: patient age, gender, weight, height, medical history and comorbidities; healthcare institution exposure for >48 h within 90 days before hospital admission; administration of antibiotics within 90 days prior to index culture collection; length of hospitalisation prior to collection of the index culture; hospital unit residence at time of index culture collection; creatinine clearance (CrCl) as estimated by the Cockcoft–Gault formula at time of index culture collection; illness severity; antibiotic treatment data (date, dose and duration); vancomycin level used (date, time and temporal relationship to vancomycin dose); microbiological data (specimen type, colony counts, vancomycin MIC as determined by Etest and co-infection pathogen); chest radiography findings; and outcome. Illness severity was calculated using both Acute Physiological and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores. Antibiotics administered in combination with vancomycin for ≥48 h were also recorded.

Microbiological data

Acceptable culture sources included expectorated sputum, endotracheal aspirate specimens (MRSA concentration $\geq 10^6$ cfu/ml), broncho-alveolar lavage (BAL) fluid (MRSA concentration $\geq 10^4$ cfu/ml), pleural fluid and blood cultures. All *S. aureus* isolates were identified by morphological analysis of colonies, Gram staining and catalase and coagulase tests. Isolates were initially tested for susceptibility to oxacillin according to Clinical and Laboratory Standards Institute (CLSI) guidelines. All *S. aureus* isolates were screened using brain heart infusion agar containing 4 μg/mL vancomycin. Vancomycin MICs were determined by the Etest (range 0.016–256 μg/mL) (AB BIODISK, Solna, Sweden) according to the manufacturer's instructions. Reference strains ATCC (American Type Culture Collection) 29213 and ATCC 43300 were used for quality control.

Outcome variables and definitions

Primary outcomes were clinical response and relapse of MRSA pneumonia within 28 days after vancomycin discontinuation. Secondary outcomes included duration of mechanical ventilation, length of hospital stay, length of ICU stay, 28-day mortality and in-hospital mortality. Patients were divided into two subgroups based on the vancomycin MICs of their MRSA isolates. Strains with vancomycin MICs of 1.5 or 2 μg/mL were placed in the high-MIC subgroup, and strains with MICs of 0.5, 0.75 or 1 μg/mL were placed in the low-MIC subgroup [11–14]. Clinical responses were assessed 5 days after the start of vancomycin treatment and at the end of therapy. Early clinical response was defined as CPIS ≤ 6 or a reduction in CPIS ≥ 2 compared with baseline and 5 days after the start of vancomycin treatment. Final clinical response (at the end of therapy) was defined as resolution of clinical signs and symptoms of pneumonia compared with baseline. Relapse of MRSA pneumonia was defined as recurrence of pneumonia with the same organism within 28 days after discontinuation of therapy.

Statistical analyses

Categorical variables were compared by the chi-squared test or Fisher's exact test, and continuous variables were compared by Student's *t* test or the Mann–Whitney *U* test. Bivariate logistic regression analysis for clinical response, relapse and in-hospital mortality was performed, and variables showing *p* value <0.25 were included in multivariate logistic regression analysis in search of independent predictors for clinical response, relapse and in-hospital mortality. In all analyses, $p < 0.05$ was considered significant when two-tailed tests were performed. All statistical procedures were performed using SPSS software (version 12.0 for Windows; SPSS, Inc., Chicago, IL, USA).

Results

During the study period, a total of 79 MRSA nosocomial pneumonia episodes occurred, and these respiratory samples underwent vancomycin MIC testing by the Etest method. Of these, nine were excluded, including four from patients with CPIS score <6, four from patients who were treated for <48 h and one from a patient whose condition did not meet the definition of nosocomial pneumonia. MRSA isolates were obtained from endotracheal aspirate specimens of 33 of the remaining 70 patients (47.1%), from BAL fluid specimens of 30 (42.9%), from sputum specimens of 6 (8.6%) and from pleural fluid of 1 patient (1.4%). Of the 70 patients with MRSA pneumonia, 15 (21.4%) also had MRSA bacteraemia, and 21 (30%) were co-infected with other bacteria, the most common being *Acinetobacter baumannii* (5/70), *Klebsiella pneumoniae* (4/70) and *Pseudomonas aeruginosa* (3/70).

The distribution of vancomycin MICs is shown in Fig. 1. Thirty-four isolates (48.6%) had high vancomycin MICs, whereas the MICs of 36 isolates (51.4%) were low. No MRSA isolates had vancomycin MIC >2 μg/mL. Mean ± standard deviation (SD) age of the 70 patients was 67.0 ± 10.7 years. The most common comorbidities were malignancy (35.7%), cerebrovascular accident (30%) and chronic lung disease (22.9%). Mean ± SD APACHE II score at ICU admission was 25.9 ± 7.3. Forty-one patients (58.6%) had ventilator-associated pneumonia. There were no significant differences in the baseline characteristics between the low- and high-MIC patient groups (Table 1).

Sixty-five (92.9%) patients received vancomycin monotherapy (15 mg/kg IV every 12 h), whereas 5 (7.1%) received a combination of vancomycin and

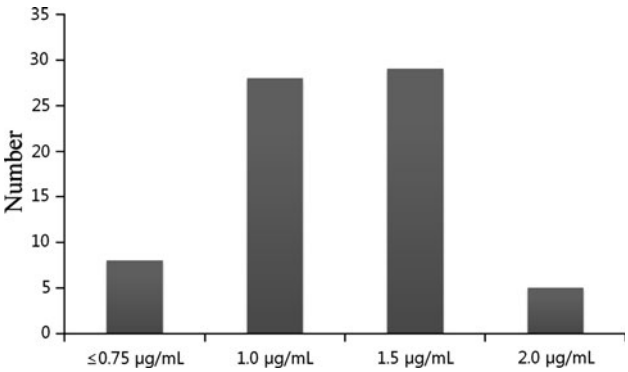

Fig. 1 Distribution of vancomycin MICs among patients ($N = 70$)

Table 1 Baseline demographic features of the low and high vancomycin MIC groups

Characteristic	Low MIC ($n = 36$)	High MIC ($n = 34$)	p-Value
Age (years), mean ± SD	65.5 ± 11.9	69.3 ± 9.1	0.139
Sex, male, *N* (%)	29 (80.6)	26 (76.5)	0.677
BMI (kg/m^2), mean ± SD	21.5 ± 4.1	22.1 ± 4.2	0.577
Underlying disease, *N* (%)			
Cerebrovascular accident	9 (25)	12 (35.3)	0.348
Malignancy	14 (38.9)	11 (32.4)	0.568
Pulmonary disease	6 (16.7)	10 (29.4)	0.204
Cardiovascular disease	5 (13.9)	3 (8.8)	0.506
Liver disease	0	1 (2.9)	0.486
Renal disease	1 (2.8)	0	1.00
Other	4 (11.1)	3 (8.8)	0.750
History of hospitalisation previous 90 days, *N* (%)	21 (58.3)	24 (70.6)	0.285
Recent antibiotics previous 90 days, *N* (%)	31 (86.1)	27 (79.4)	0.457
Recent vancomycin previous 90 days, *N* (%)	8 (22.2)	8 (23.5)	0.896
Length of stay (days) prior to MRSA pneumonia, median (IQR)	12 (6–26)	12 (5–20)	0.445
Hospital unit residence at time of index culture collection, *N* (%)			
Long-term care facility	2 (5.6)	3 (8.8)	0.669
General ward	8 (22.2)	6 (17.6)	0.768
Intensive care unit	26 (72.2)	25 (73.5)	0.902
On mechanical ventilation	21 (58.3)	18 (52.9)	0.650
Ventilator-associated pneumonia, *N* (%)[a]	22 (61.1)	19 (55.9)	0.657
APACHE II score, mean ± SD[b]	25.6 ± 6.9	26.1 ± 7.9	0.799
APACHE II score ≥25, *N* (%)[b]	19 (54.3)	16 (51.6)	0.828
SOFA score, mean ± SD	7.5 ± 3.4	7.5 ± 4.5	0.963
CPIS, mean ± SD	8.5 ± 1.9	8.8 ± 1.9	0.557
WBC (×10^3/mm^3), mean ± SD	13.8 ± 6.5	14.5 ± 9.8	0.706
CRP (mg/dL), mean ± SD	15.2 ± 11.9	10.6 ± 7.5	0.059
PaO_2/FiO_2 (mmHg), mean ± SD	200.5 ± 111.5	199.8 ± 102.8	0.977
CrCl ≤33 ml/min, *N* (%)	5 (13.9)	4 (11.8)	0.791
Co-infection, *N* (%)	12 (33.3)	9 (26.5)	0.531
MRSA bacteraemia, *N* (%)	10 (27.8)	5 (14.7)	0.183
Septic shock, *N* (%)	20 (55.6)	17 (50.0)	0.642

APACHE II Acute Physiology and Chronic Health Evaluation II, *BMI* body mass index, *CPIS* clinical pulmonary infection score, *CrCl* creatinine clearance, *CRP* C-reactive protein, *IQR* interquartile range, *MIC* minimum inhibitory concentration, *MRSA* methicillin-resistant *Staphylococcus aureus*, *N* number, *SD* standard deviation, *SOFA* Sequential Organ Failure Assessment, *WBC* white blood cell

[a] Ventilator-associated pneumonia: pneumonia developing more than 48 h after endotracheal intubation

[b] $N = 66$; four patients were excluded because of missing data

rifampicin (15 mg/kg IV plus rifampicin 300 mg p.o. every 12 h). Two patients discontinued vancomycin therapy within 72 h; of these, one was changed to an alternative agent and the other died. An additional 14 patients were switched to an alternative anti-MRSA agent within 7 days of starting vancomycin. The switch to an alternative anti-MRSA agent was somewhat more frequent in the high- than in the low-MIC group (26.5% versus 16.7%), but this difference was not significant ($p = 0.318$). Vancomycin trough levels were available for 57 patients. The rate of achievement of a trough level above 15 mg/L within 72 h, the frequency of delayed vancomycin administration and the median duration of vancomycin administration did not differ significantly between the two groups (Table 2). All patients who had concurrent infections with other organisms received adequate antibiotic therapy.

The early clinical response rate on day 5 was significantly higher in the low- than in the high-MIC group [63.9% (23/36) versus 35.3% (12/34), $p = 0.031$] (Fig. 2). However, the final clinical response rate at the end of therapy was similar in the two groups [72.2% (26/36) versus 64.7% (22/34), $p = 0.609$]. The relapse rate of MRSA pneumonia within 28 days after vancomycin discontinuation was significantly higher in the high- than in the low-MIC group [29.6% (8/27) versus 6.9% (2/29), $p = 0.038$]. The overall in-hospital mortality rate was 32.9%, but the 28-day and in-hospital mortality rates did not differ between the two groups (Table 3). Although the differences were not statistically significant, patients in the high-MIC group had longer hospital stays (5 days), longer ICU stays (4 days) and longer duration of mechanical ventilation (5 days).

Fifteen patients were switched to an agent other than vancomycin within 7 days; 12 were switched to linezolid and 3 to teicoplanin. Of these, 12 (80%) responded favourably to the alternative agent, whereas 3 (1 switched to linezolid and 2 switched to teicoplanin) failed treatment and ultimately died within 28 days. Overall, 20 patients received haemodialysis, 8 of whom had

Table 2 Treatment-related factors of the low- and high-MIC groups

Variable	Low MIC ($n = 36$)	High MIC ($n = 34$)	p-Value
First treatment regimen, *N* (%)			0.669
Vancomycin single	34 (94.4)	31 (91.2)	
Vancomycin + rifampicin	2 (5.6)	3 (8.8)	
Delayed vancomycin administration, *N* (%)	10 (27.8)	6 (18.2)	0.345
Duration of vancomycin administration, median (IQR)	13 (8–22)	12 (7–19)	0.334
Vancomycin trough level within 72 h ≥15 mg/L, *N* (%)[a]	19 (67.9)	16 (55.2)	0.325
Switched to alternative antibiotics, *N* (%)	6 (16.7)	9 (26.5)	0.318
Teicoplanin	2 (5.6)	1 (2.9)	
Linezolid	4 (11.1)	8 (23.6)	
Concomitant antibiotics, *N* (%)			
Carbapenem	10 (27.8)	16 (47.1)	0.095
Piperacillin–tazobactam	9 (25)	5 (14.7)	0.374
Third- or fourth-generation cephalosporins	3 (8.3)	7 (20.6)	0.182
Levofloxacin	8 (22.2)	2 (5.9)	0.085
Colistin	2 (5.6)	1 (2.9)	1.00
Carbapenem + levofloxacin	2 (5.6)	1 (2.9)	1.00
Piperacillin–tazobactam + levofloxacin	0	1 (2.9)	0.486

IQR interquartile range, *MIC* minimum inhibitory concentration, *N* number
[a] This value is available in only 57 patients

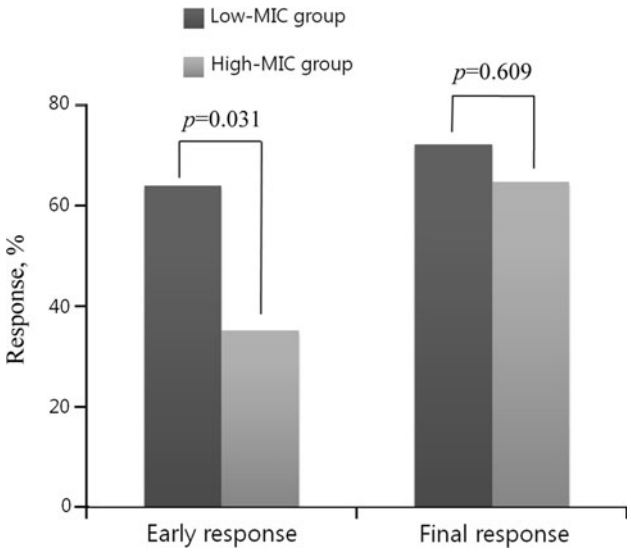

Fig. 2 Early and final clinical responses in patients infected with MRSA strains with low (0.5–1.0 μg/mL) and high (≥1.5 μg/mL) vancomycin MICs. Early clinical response was assessed 5 days after start of vancomycin treatment. Final clinical response was assessed at end of therapy

pre-existing renal disease. During the course of treatment, four patients in the low-MIC group and two in the high-MIC group became infected by a vancomycin-resistant enterococcus or fungus. No other serious adverse events occurred.

On multivariate analysis, ICU residence at time of index culture collection and infection caused by high-MIC strains were significantly associated with early clinical response failure (Table 4). Additionally, administration of antibiotics within 90 days prior to index culture collection was an independent predictor of final clinical response failure (Table 5). However, infection caused by high-MIC strains was not an independent predictor of final clinical response failure or relapse of MRSA pneumonia when controlling for APACHE II score, carbapenem combination, attainment of target trough concentration, switch to linezolid therapy, bacteraemia, septic shock and ventilator-associated pneumonia on multivariate logistic regression analysis. On multivariate logistic regression analysis, only APACHE II score [odds ratio (OR) 1.194; 95% confidence interval (CI) 1.037–1.374, $p = 0.014$] was an independent predictor of in-hospital mortality after controlling for age, vancomycin MIC, co-infection, carbapenem combination, switch to linezolid therapy, septic shock, ventilator-associated pneumonia and attainment of target trough concentration.

Discussion

We found that patients with MRSA nosocomial pneumonia showed a low clinical response rate and a high relapse rate when treated with vancomycin. About half of the MRSA isolates had high vancomycin MICs (≥1.5 μg/mL). Although these MICs were in the "susceptible" range, patients infected with these isolates showed a poorer clinical response and a higher relapse rate than did patients infected with isolates with low vancomycin MIC. In particular, infection caused by high-MIC strains was an independent predictor of early clinical response failure.

We defined high vancomycin MICs as those ≥1.5 μg/mL. The definition of high vancomycin MIC has differed in various studies of patients with MRSA bacteraemia [10–14]; for example, when high vancomycin MIC was

Table 3 Comparisons of outcomes in the low and high vancomycin MIC groups

Outcome	Low MIC ($n = 36$)	High MIC ($n = 34$)	p-Value
Duration to culture negative (days), median (IQR)	9 (6–14)	10 (5–15)	0.844
Early clinical response rate, *N* (%)	23 (63.9)	12 (35.3)	0.031
Final clinical response rate, *N* (%)	26 (72.2)	22 (64.7)	0.609
Relapse of MRSA pneumonia within 28 days, *N* (%)[a]	2 (6.9)	8 (29.6)	0.038
28-day mortality, *N* (%)[b]	6 (17.1)	4 (12.9)	0.632
In-hospital mortality, *N* (%)	11 (30.6)	12 (35.3)	0.673
Length of hospital stay (days), median (IQR)			
Total length of hospital stay	63 (42–111)	62 (38–89)	0.686
Total length of hospital stay after MRSA pneumonia	42 (26–74)	47 (26–72)	0.845
Number of patients in the ICU (%)	35 (97.2)	30 (88.2)	0.192
Length of ICU stay (days), median (IQR)			
Total length of ICU stay	22 (16–55)	23 (12–40)	0.630
Total length of ICU stay after MRSA pneumonia	16 (11–32)	20 (10–40)	0.688
Number of patients on the ventilator (%)	29 (80.6)	26 (76.5)	0.677
Duration of mechanical ventilation (days), median (IQR)			
Total duration	18 (12–42)	19 (9–38)	0.587
Duration after MRSA pneumonia	11 (7–22)	16 (3–31)	0.90
Adverse events			
Haemodialysis, *N* (%)	13 (36.1)	7 (20.6)	0.151
Superinfection, *N* (%)	4 (11.1)	2 (5.9)	0.674
Vancomycin-resistant enterococcus	2	1	
Fungus (*Aspergillus* species)	1	1	
Cytomegalovirus	1	0	

IQR interquartile range, *MIC* minimum inhibitory concentration, *MRSA* methicillin-resistant *Staphylococcus aureus*, *MV* mechanical ventilation, *N* number

[a] Low MIC: seven patients were excluded because six died and one was transferred within 28 days. High MIC: seven patients were excluded because four died and three were transferred within 28 days

[b] Low MIC: one patient was excluded because of transfer within 28 days. High MIC: three patients were excluded because of transfer within 28 days

Table 4 Multivariate logistic regression analysis of factors associated with early clinical response failure of patients with MRSA nosocomial pneumonia

Factor	OR (95% CI)	p-Value
ICU residence at time of index culture collection	4.941 (1.231–19.827)	0.024
High vancomycin MIC strain	3.700 (1.130–12.109)	0.031
MRSA bacteraemia	2.320 (0.528–10.205)	0.265
Septic shock at diagnosis	1.802 (0.534–6.084)	0.343
Carbapenem combination	0.992 (0.284–3.468)	0.991
Vancomycin trough level within 72 h ≥15 mg/L	1.930 (0.366–10.164)	0.438
Haemodialysis	2.088 (0.507–8.603)	0.308

CI confidence interval, *ICU* intensive care unit, *MIC* minimum inhibitory concentration, *MRSA* methicillin-resistant *Staphylococcus aureus*, *OR* odds ratio

defined as ≥2 μg/mL, isolates from 54% [10] to 22.2% [11] of patients with MRSA bacteraemia had high vancomycin MICs. In the present study, however, only 7% of isolates had vancomycin MICs of 2 μg/mL, with most isolates in this study showing moderate increases in MIC (1–1.5 μg/mL). Patients with MRSA bloodstream infections with vancomycin MICs ≥1.5 or 2 μg/mL have been found to respond poorly to vancomycin [10, 12–14]. Patients infected with MRSA isolates with vancomycin MICs >1 μg/mL may respond better to combination therapies or linezolid [16–21].

The final response rate observed, about 68.6%, was comparable to the rates seen in clinical trials with hospitalised adults with MRSA infections [10, 17, 19, 21]. However, we found that our high vancomycin MIC group had an early clinical response rate of 35.3%, despite a final clinical response rate at the end of therapy of 64.7%. Between-group differences were observed only in the early clinical response rate and not in the final clinical response rate. Several explanations may be proposed for this result. First, the early response may have been poor in the high-MIC group because the bactericidal activity of

Table 5 Multivariate logistic regression analysis of factors associated with final clinical response failure of patients with MRSA nosocomial pneumonia

Factor	OR (95% CI)	*p*-Value
Recent antibiotics previous 90 days	18.339 (1.056–318.472)	0.046
APACHE II	1.078 (0.969–1.200)	0.168
High vancomycin MIC strain	1.312 (0.289–5.954)	0.725
MRSA bacteraemia	1.111 (0.170–7.260)	0.912
Septic shock at diagnosis	2.030 (0.442–9.323)	0.363
Ventilator-associated pneumonia	1.745 (0.347–8.783)	0.449
Carbapenem combination	0.264 (0.062–1.133)	0.073
Vancomycin trough level within 72 h ≥15 mg/L	0.218 (0.031–1.514)	0.123
Switched to linezolid	0.622 (0.112–3.472)	0.589

APACHE II Acute Physiology and Chronic Health Evaluation II, *CI* confidence interval, *MIC* minimum inhibitory concentration, *MRSA* methicillin-resistant *Staphylococcus aureus*, *OR* odds ratio

vancomycin is slow against strains with high MICs. A report using a mouse peritonitis model [22] to compare the efficacy of antibacterial glycopeptides against strains of four different MICs showed that bactericidal activity decreased significantly with slight increases in glycopeptide MIC. In addition, the median time to bacterial clearance was significantly longer for MRSA isolates with vancomycin MICs of 2 μg/mL compared with those with MICs of <1 μg/mL [14]. Second, although all strains were susceptible to vancomycin, the populations may be heterogeneous, with some bacteria showing greater resistance to vancomycin [heteroresistant vancomycin-intermediate *Staphylococcus aureus* (hVISA) organisms] [23, 24]. Some hVISA strains were found to have vancomycin MICs ≤2 μg/mL, as determined by the broth dilution method or Etest, rendering them "susceptible" according to current CLSI interpretive criteria [25, 26]. The prevalence of hVISA was higher among isolates with vancomycin MICs of 2 μg/mL than among strains with lower MICs [25]. Third, the area under the concentration curve divided by the MIC (AUC/MIC) has been shown to be the best predictor of vancomycin activity against *S. aureus*; for example, a study of the relationship between vancomycin AUC/MIC and outcomes in patients with lower respiratory tract infections caused by *S. aureus* and treated with vancomycin showed that AUC/MIC value ≥350 was independently associated with clinical success (OR 7.19) [27]. When a vancomycin trough serum concentration of 15 mg/L was chosen, the probabilities of achieving this AUC/MIC target at MIC values of 1 and 2 μg/mL were 60% and 0%, respectively [28, 29]. Although we did not evaluate hVISA phenotype or AUC/MIC, the factors discussed above may be associated with the poor early clinical response to vancomycin observed in our high-MIC group.

Although the final clinical response rate was about 8% lower in the high- than in the low-MIC group, the difference was not statistically significant. Moreover, there were no between-group differences in mortality rates or other secondary outcome variables. These findings differ from those reported previously; for example, treatment failure was 2.4-fold higher in patients infected with strains with vancomycin MICs ≥1.5 μg/mL than in patients infected with strains having vancomycin MICs of ≤1 μg/Ml [12]. Moreover, multivariate analysis showed that high MIC was an independent predictor of poor treatment response [10]. In addition, mortality rates associated with MRSA bacteraemia were significantly higher in patients infected with strains with vancomycin MICs of 2 μg/mL (OR 6.39) [11]. The similar final clinical responses and mortality rates observed in our two groups may have been associated with the switching of patients who showed poor early clinical responses (at 5 days) to an alternative bactericidal agent within 7 days, whereas the relatively good initial responders were continued on vancomycin. Of the patients who were switched to alternative agents, 80% responded favourably. Second, only 7% of our patients had strains with a vancomycin MIC of 2 μg/mL.

The relapse rate of MRSA pneumonia within 28 days after discontinuation of therapy was higher in the high- than in the low-MIC group (29.6% versus 6.9%). Although only a few studies have reported relapse rates in patients with MRSA nosocomial infection, such infections often recur [30], suggesting that vancomycin has a suboptimal antimicrobial action against high-MIC strains. Overall, these findings suggest the need for alternative or combination therapies to combat invasive infections caused by MRSA strains with high vancomycin MICs.

Our study had several limitations. First, the work was retrospective in design, possibly introducing a selection bias. Second, the number of patients enrolled was small, making statistical calculations problematic, especially when assessing secondary outcomes such as mortality. Third, we included some patients infected with multidrug-resistant pathogens such as carbapenem-resistant *Acinetobacter baumannii* and extended-spectrum beta-lactamase-positive Gram-negative organisms. Although these infections were successfully treated with the appropriate antibiotics, the presence of these infections

may have been a confounding factor. Also, because this was not a prospective trial, measurements of vancomycin concentrations in serum were available for only 57 patients. Another confounding factor may be the low rate of achievement of trough serum vancomycin concentrations >15 mg/L.

In conclusion, our findings suggest that, overall, patients with MRSA nosocomial pneumonia respond poorly to vancomycin. About half of the MRSA isolates from patients with nosocomial pneumonia had high vancomycin MICs (≥1.5 μg/mL). Although such MRSA strains are within the "susceptible" range, patients infected with such strains showed a slower clinical response and a higher relapse rate than did patients infected with strains with low vancomycin MICs.

Acknowledgments We thank H. Kil and E.M. Jo for their assistance in the statistical review and the preparation of the manuscript. We also acknowledge the informative and insightful review by an anonymous reviewer. This study was supported by a grant of the Korea Healthcare Technology R&D Project, Ministry for Health, Welfare and Family Affairs, Republic of Korea (A084063).

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