a pressure ulcer. Moreover, the anatomic location of a pressure ulcer may be a critical factor in the development of necrotizing STIs because the opportunity for fecal infection is higher for sacral and coccygeal pressure ulcers [11]. The necrotizing STIs developed from pressure ulcers demonstrated mainly polymicrobial infections, with both aerobic and anaerobic pathogens frequently observed in the chronic wounds [12,13].

Although the cases reported in present study involved elderly patients with multiple comorbidities, the mortality rate was lower than that reported previously [14]. One of the reasons for the lower mortality rate was that surgical intervention (debridement) was performed in 23 of the 24 cases at the initial stage. Another reason might be the appropriate use of broad-spectrum antibiotics to treat the multiple pathogens associated with these infections.

This study was conducted in a limited number of patients; however, it provides information regarding the characteristics of these necrotizing STIs that develop from pressure ulcers. This important complication needs to be recognized in order to achieve effective management of pressure ulcers.

## Conflict of interest

The authors declare that they have no conflicts of interest.

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Clinical Interventions in Aging

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ORIGINAL RESEARCH

# Pharmacodynamics of vancomycin in elderly patients aged 75 years or older with methicillin-resistant *Staphylococcus aureus* hospital-acquired pneumonia

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**Background:** Methicillin-resistant *Staphylococcus aureus* (MRSA) infections are associated with significant mortality and health care costs. To improve treatment outcomes for MRSA, a better understanding of the pharmacokinetic/pharmacodynamic parameters of vancomycin is required to develop optimal dosing strategies, particularly in elderly patients (≥75 years of age) with limited renal function. The purpose of this study was to determine whether pharmacokinetic indices for vancomycin are associated with mortality from MRSA hospital-acquired pneumonia in elderly patients.

**Methods:** We conducted a retrospective observational study with 28-day mortality as the primary outcome for 94 patients with MRSA hospital-acquired pneumonia who had been treated with vancomycin from January 2006 through December 2012. Our most recent sampling of MRSA isolates had a minimum inhibitory concentration (MIC) for vancomycin of 1 μg/mL (86%), indicating that the area under the curve (AUC) was equal to the AUC/MIC in these isolates. The primary data from 28-day survivors and nonsurvivors were compared.

**Results:** Among 94 elderly patients, the mean age was 82 (75–99) years. Multivariate analyses revealed that, among the factors examined, only the nonoptimal AUC (<250, >450 μg*h/mL) was an independent predictor of 28-day mortality in elderly patients (odds ratio 23.156, 95% confidence interval 6.814–78.687, $P < 0.001$). We detected a significant difference for increasing nephrotoxicity in nonsurvivors (nine of 32 patients [28%]) compared with survivors (three of 62 patients [4.8%], $P = 0.003$).

**Conclusion:** This finding indicates that patients with potentially poor renal function are likely to have increased AUC values and a poor prognosis. Consideration of the pharmacokinetics/pharmacodynamics of vancomycin and targeting an AUC/MIC value of 250–450 μg*h/mL may result in improved treatment outcomes for elderly patients with MRSA hospital-acquired pneumonia.

**Keywords:** methicillin-resistant *Staphylococcus aureus*, elderly patients, vancomycin, pharmacokinetics, pharmacodynamics

## Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) infections are associated with significant mortality and health care costs.[1] In nearly all hospitals, MRSA has become one of the Gram-positive bacterial species associated with serious hospital-acquired infections.[2–9] The population of patients most vulnerable to acquiring MRSA infections, including hospital-acquired pneumonia, is the elderly, whose immune systems are often affected by aging, underlying diseases, and medical interventions. In Japan, senior

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citizens aged 75 years and older, termed elderly, constitute over 10.4% of the population and represent the largest and most frequent users of health care facilities, such as hospitals and long-term skilled nursing and residential homes. Improving treatment outcomes for elderly patients with MRSA infections will therefore increase survival and quality of life, and reduce health care expenditure burdens.[2]

To date, MRSA hospital-acquired pneumonia has primarily been treated with intravenously administered vancomycin. In vitro and animal model studies investigating the pharmacodynamics of vancomycin indicate that the rate of MRSA killing depends primarily upon the duration of exposure to concentrations exceeding the minimum inhibitory concentration (MIC) value of the target strain. Although the area under the curve (AUC)/MIC ratio is the best predictor of efficacy in animal models,[10,11] data characterizing the pharmacodynamic properties of vancomycin against MRSA in humans are limited. Although a study that examined clearance of MRSA from sputum suggested that an AUC/MIC ratio >400 may be effective,[12] a study involving adult patients with MRSA pneumonia or sepsis failed to show an association between pharmacokinetic/pharmacodynamic parameters of vancomycin and treatment outcomes.[13]

In elderly individuals, renal clearance is significantly reduced. Creatinine clearance decreases with age but serum creatinine concentration remains relatively stable because elderly persons typically lose muscle mass as they age, often leading to overestimation of renal function in the elderly.[14–17] Because vancomycin is eliminated from the body mainly via the kidneys, overestimation of renal function leads to increased vancomycin trough concentrations, which may result in nephrotoxicity. However, it is uncertain whether targeting higher blood concentrations leads to increased efficacy of vancomycin and/or risk of nephrotoxicity in elderly patients. We performed a retrospective observational study to determine whether two pharmacokinetic indices for vancomycin, ie, serum trough concentrations and AUC values, are associated with mortality from MRSA hospital-acquired pneumonia in elderly patients aged 75 years and older.

## Materials and methods

### Study location and patients

The study was conducted at the National Center for Geriatrics and Gerontology Hospital, Obu, Japan. This 320-bed hospital comprises general (including emergency) services, except for pediatrics, and admits approximately 5,000 patients per year (more than 50% of whom are aged over 75 years). MRSA is endemic in this hospital, and the ratio of MRSA isolates per total *S. aureus* isolates is approximately 70%.

During a 6-year period (from January 2006 through December 2012), all hospitalized patients aged 75 years or older with MRSA pneumonia microbiologically confirmed by sputum or blood cultures and treated with vancomycin therapy were identified using the clinical pharmacokinetics department computer database.

### Study design and data collection

We conducted a retrospective 6-year observational study with 28-day mortality as the primary outcome for 94 patients with MRSA pneumonia treated using vancomycin. We also assessed the relationship between the effect of pharmacokinetic indices of vancomycin, including serum trough concentrations and AUC values, and the primary outcome. The clinical characteristics of the study patients were reviewed from hospital medical records. For patients with multiple episodes, only the first episode was counted. This study was approved by the ethics committee at the National Center for Geriatrics and Gerontology Hospital.

### Definitions

The definition of hospital-acquired pneumonia was based on American Thoracic Society guidelines for the management of adults with hospital-acquired, ventilator-associated, and health care-associated pneumonia.[2] Here, hospital-acquired pneumonia was defined as pneumonia occurring 48 hours or more after hospitalization, with an acute lung infection characterized by cough, fever, purulent sputum, and an abnormal chest X-ray, that was not deemed to be incubating at the time of admission. Among hospital-acquired pneumonia cases, those with MRSA isolated from blood culture or sputum which showed no sign of improvement after treatment with broad-spectrum antibiotics, such as carbapenem, for more than 3 days were defined as MRSA hospital-acquired pneumonia.

The severity rating of pneumonia was defined according to the Japanese Respiratory Society guidelines for management of hospital-acquired pneumonia[18] and was used to divide the patients into severe, moderate, and mild groups. The severe group was defined as patients with three or more of the following risk factors or conditions: malignancy or immunocompromised status, impaired consciousness, requiring a fraction of inspired oxygen >35% to maintain oxygen saturation >90%, mean age 70 years or older (woman aged 75 years or older), and oliguria or dehydration. The moderate group was defined as patients with any two of the risk factors described above, and

in addition, at least one of the following secondary risk factors: C-reactive protein ≥20.0 mg/L or extent of infiltration on chest X-ray covering at least two thirds of one lung. The mild group was defined as all other patients who were not compatible with severe or moderate criteria. Immunosuppression was defined as need for corticosteroids or immunosuppressive agents.[2] Nephrotoxicity resulting from treatment with vancomycin was defined as an increase in serum creatinine of 0.5 mg/dL or a 50% increase from pretreatment levels.[10] Patients were divided into 28-day survivors and nonsurvivors from the time of vancomycin administration.

## Microbiologic data

Our institutional microbiology laboratory performed antimicrobial susceptibility tests of clinical isolates using a broth microdilution method with the MicroScan Pos Series PC6.1J panel (Siemens, Sacramento, CA, USA) according to Clinical Laboratory and Standards Institute recommendations.[19] To determine more accurately the susceptibility of MRSA to vancomycin, the most recent (January 2010 through December 2012) MRSA samples collected from patients (n = 21) were sent to Mitsubishi Chemical Medience Corporation (Tokyo, Japan) for determination of a vancomycin MIC ranging from 0.5 to 2.0 μg/mL.

## Pharmacokinetic data

The initial treatment schedule for vancomycin was simulated to achieve a trough concentration of 10–15 μg/mL with TDM software, using patient characteristics, including age, body weight, and serum creatinine (VCM-TDM Microsoft Excel version 3.0, Shionogi and Co, Ltd, Osaka, Japan). Serum concentrations of vancomycin were determined from samples collected on the fifth day from the start of drug administration. Blood samplings were performed twice, ie, once before vancomycin administration (trough), and once one hour after vancomycin administration (peak). The predicted 24-hour AUC values for vancomycin were calculated using TDM software based on peak and trough concentrations.

## Statistical analysis

All comparisons were unpaired, and all tests of significance were two-tailed. Continuous variables were compared using the Student's *t*-test for normally distributed variables and the Mann-Whitney *U* test for non-normally distributed variables. Categorical variables were compared using the Chi-square or Fisher's Exact tests. The primary data from 28-day survivors and nonsurvivors were compared. The multivariable model was used to establish risk factors for mortality after treatment with vancomycin for MRSA pneumonia. Multivariable analysis were used for nephrotoxicity, the Charlson comorbidity index, and nonoptimal AUC.[16] The predictive ability of the final model was quantified using Hosmer–Lemeshow statistical tests for goodness of fit. In these tests, a two-sided *P*-value of less than 0.05 was considered to be statistically significant. Statistical package for the Social Sciences SPSS version 12.0 software (SPSS Inc, Chicago, IL, USA) was used for the statistical analysis.

# Results

Ninety-four elderly patients aged 75 years or older with MRSA pneumonia treated using vancomycin were eligible for the study. The median age of the study patients was 82 (range 75–99) years, with more than half of the patients (71/94 [76%]) residing in a nursing facility before hospital admission. Of the 94 patients, 18 (19%) had MRSA pneumonia and sepsis, while the remaining 76 (81%) were diagnosed with MRSA pneumonia without sepsis. MRSA was coisolated with *Pseudomonas aeruginosa* (n = 6) and/or *Klebsiella pneumoniae* (n = 8) and/or *Acinetobacter* species (n = 7) in 21 of 94 patients (22%). All patients had at least one comorbid disease, such as cardiovascular disease, dementia, or diabetes mellitus (data not shown).

The demographic data of the 28-day survivors (n = 62) and nonsurvivors (n = 32) are summarized in Table 1. The percentage of severe cases among survivors was 45%

**Table 1** Characteristics of study patients with methicillin-resistant *Staphylococcus aureus* pneumonia

| Characteristic | Survivors (n = 62) | Nonsurvivors (n = 32) | *P*-value |
|---|---|---|---|
| Age (years) | 83.0 ± 6.2 (75–99) | 81.8 ± 5.2 (75–93) | 0.162[a] |
| Gender (male/female) | 39/23 | 24/8 | 0.171[b] |
| Body weight (kg) | 43.1 ± 9.2 (27–70) | 42.5 ± 9.4 (28–72) | 0.388[a] |
| Serum creatinine (mg/dL) | 0.7 ± 0.4 (0.2–2.5) | 0.8 ± 0.4 (0.2–2.1) | 0.145[a] |
| Charlson comorbidity index | 2.4 ± 1.8 (0–8) | 3.1 ± 2.5 (1–10) | 0.089[b] |
| Combination antibiotic therapy | 32 (51.6%) | 20 (63%) | 0.216[b] |
| Diagnosis | | | |
| Pneumonia/Pneumonia and sepsis | 48/14 | 28/4 | 0.185[b] |
| Infection severity | | | |
| Mild | 9 | 4 | 0.004[c]* |
| Moderate | 25 | 3 | |
| Severe | 28 | 25 | |

**Notes:** [a]*P*-values were determined by the Student's *t*-test; [b]Fisher's Exact test; [c]Chi-square test. *$P < 0.01$, survivors versus nonsurvivors. Data are presented as the mean ± standard (range) deviation or the number of subjects (percentage).

(28/62), whereas the rate was 78% (25/32) among nonsurvivors ($P$ = 0.004). Mean (± standard deviation [range]) serum creatinine levels in the survivor group was 0.7 ± 0.4 (0.2–2.5) mg/dL while that in the nonsurvivor group was 0.8 ± 0.4 (0.2–2.1) mg/dL ($P$ = 0.145). Survivors tended to have a lower mean Charlson comorbidity index (2.4 ± 1.8 [0–8]) than nonsurvivors (3.1 ± 2.5 [1–10], $P$ = 0.089). Coexistence of MRSA bacteremia did not significantly differ between the two groups (23% versus 19%, respectively, $P$ = 0.375).

The pharmacokinetic and pharmacodynamic parameters of vancomycin in survivors and nonsurvivors are summarized in Table 2. Notably, the mean trough and peak concentrations, calculated AUC values, and clearance of vancomycin did not differ significantly between the two groups (Table 2).

Stratification of vancomycin trough concentrations revealed no statistically significant relationships with 28-day mortality at any of the breakpoints evaluated ($P$ = 0.603, Figure 1A). However, the AUC values of <250 or >450 μg*h/mL were significantly associated with 28-day mortality ($P$ < 0.001, Figure 1B).

We next investigated the risk factors for mortality after treatment of MRSA pneumonia with vancomycin (Table 3). Univariate analysis was used to compare survivors and nonsurvivors. The following risk factors were found to be associated with 28-day mortality: nephrotoxicity and Charlson comorbidity index, nonoptimal AUC (<250, >450 μg*h/mL, Table 3). These risk factors were analyzed by multivariate analysis with multiple logical regression, finding the following as 28-day mortality: nephrotoxicity ($P$ = 0.309, odds ratio [OR] 2.544; 95% confidence interval [CI] 0.421–15.371), Charlson comorbidity index ($P$ = 0.128, OR 1.236; 95% CI 0.941–1.625), nonoptimal AUC ($P$ < 0.001, OR 23.156; 95% CI 6.814–78.687, Table 3). The multiple logistic regression model was well calibrated among deciles of observed and expected risk in survivors and nonsurvivors (Hosmer–Lemeshow test, $P$ = 0.194, Table 3).

Our institutional microbiology laboratory determined that all MRSA isolates from study patients (n = 94) had a vancomycin MIC of less than 2.0 μg/mL. To determine more accurately the vancomycin MIC, recent consecutive MRSA

**Table 2** Pharmacokinetic and pharmacodynamic parameters for vancomycin between surviving and nonsurviving patients with methicillin-resistant *Staphylococcus aureus* pneumonia

| PK/PD parameters | Survivors (n = 62) | Nonsurvivors (n = 32) | P-value |
|---|---|---|---|
| $C_{max}$ (μg/mL) | 24.5 ± 8.2 | 25.5 ± 8.0 | 0.378 |
| Trough concentration (μg/mL) | 9.2 ± 8.2 | 10.0 ± 5.8 | 0.266 |
| AUC (μg*h/mL) | 344 ± 95.8 | 394.7 ± 209.9 | 0.104 |
| Vd (L) | 62.3 ± 6.6 | 63.6 ± 4.1 | 0.129 |
| $T_{1/2}$ (hours) | 26.5 ± 13.1 | 31.5 ± 23.2 | 0.064 |
| CLr (mL/min) | 40.8 ± 16.9 | 35.5 ± 18.9 | 0.094 |
| Daily dose (mg/kg/day) | 20.9 ± 10.6 | 18.8 ± 6.6 | 0.119 |
| Dose interval (hours) | 26.5 ± 13.3 | 25.5 ± 7.8 | 0.322 |

**Notes:** *P*-values were determined by the Student's *t*-test. Data were presented as the mean ± standard deviation.

**Abbreviations:** AUC, area under the curve; Vd, volume of distribution; CLr, renal clearance; PD, pharmacodynamic; PK, pharmacokinetic; $C_{max}$, concentration max; $T_{1/2}$, half-life.

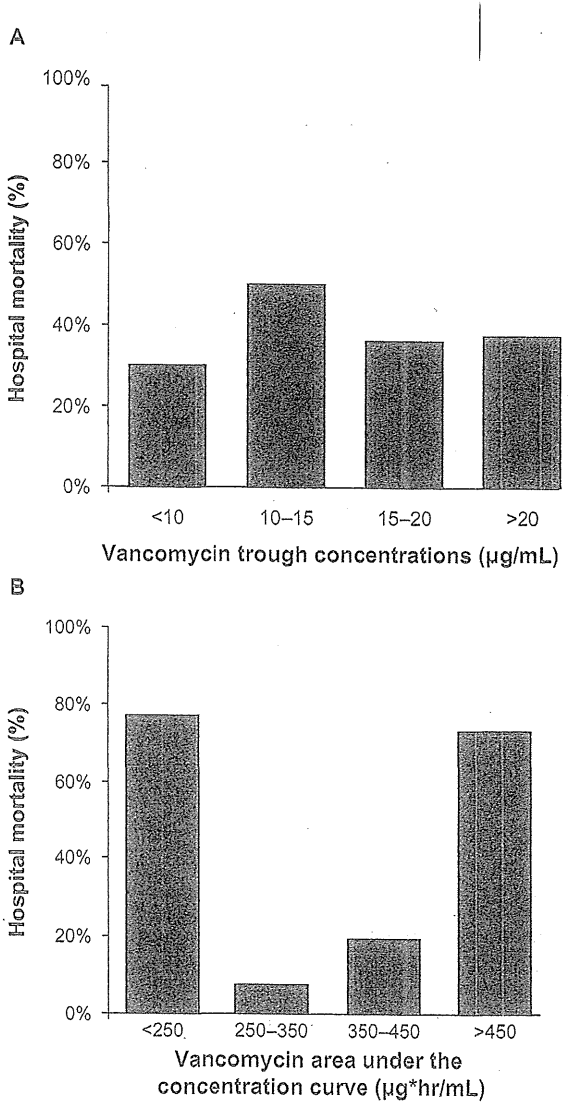


**Figure 1** Twenty-eight-day mortality according to stratification of vancomycin trough concentrations and AUC values. Data were presented as percentages. *P* values were determined by $\chi^2$ tests. Stratification of vancomycin trough concentrations revealed no statistically significant relationship with 28-day mortality at any of the breakpoints evaluated ($P$ = 0.603 [A]). However, AUC values of 250–350 μg*h/mL and 350–450 μg*h/mL were associated with significantly lower 28-day mortality than AUC values <250 and >450 μg*h/mL ($P$ < 0.001 [B]).

**Abbreviation:** AUC, area under the concentration curve.

**Table 3** Risk factors for mortality after treatment of methicillin-resistant *Staphylococcus aureus* pneumonia with vancomycin

| Variable | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | Odds ratio | 95% CI | *P*-value | Odds ratio | 95% CI | *P*-value |
| Age | 0.983 | 0.881–1.097 | 0.763 | | | |
| Nephrotoxicity | 2.570 | 0.420–15.734 | 0.307 | 2.544 | 0.421–15.371 | 0.309 |
| Infection severity | 1.021 | 0.268–3.889 | 0.976 | | | |
| Charlson comorbidity index | 1.236 | 0.924–1.654 | 0.154 | 1.236 | 0.941–1.625 | 0.128 |
| Combination antibiotic therapy | 0.745 | 0.195–2.852 | 0.667 | | | |
| Nonoptimal AUC (<250, >450 μg*h/mL) | 25.377 | 5.791–111.203 | < 0.001 | 23.156 | 6.814–78.687 | < 0.001 |

**Note:** Hosmer–Lemeshow test, $P = 0.134$.
**Abbreviations:** AUC, area under the concentration curve; CI, confidence interval.

isolates (n = 21) were sent out and subjected to susceptibility testing by the microdilution method at a commercial microbiology laboratory. The majority of isolates were determined to have a vancomycin MIC of 1 μg/mL (n = 18, 86%), with the remaining isolates having a vancomycin MIC of 0.5 μg/mL (n = 3, 14%).

We also examined adverse effects and found that 12 of 94 (13%) developed nephrotoxicity on vancomycin (Table 4). We detected a significant difference for increasing nephrotoxicity in nonsurvivors (nine of 32 patients [28%]) compared with survivors (three of 62 patients [4.8%], $P = 0.003$).

## Discussion

This retrospective observational study shows that a vancomycin AUC value of 250–450 μg*h/mL predicted 28-day mortality in elderly patients with MRSA pneumonia. Our findings suggest that a better understanding of the pharmacodynamics of vancomycin in the elderly may allow improved dosing strategies and treatment outcomes for MRSA infections in this vulnerable population.

There are studies[20–22] showing that bacteremia during MRSA hospital-acquired pneumonia impacts on the prognosis, and comorbid conditions such as malignancy lead to a poor outcome.[20] Among the elderly patients with MRSA pneumonia examined in our study, many had severe comorbid conditions, such as malignancy, cardiovascular disease, and severe diabetes mellitus (Table 1). Further, the Charlson comorbidity index tended to be higher in nonsurvivors compared with survivors. In addition, in univariate analyses, the percentage of patients with sepsis was not significantly different between survivors and nonsurvivors, and the percentage of severe cases among nonsurvivors was higher than that among survivors ($P = 0.004$, Table 1). However, no significant differences in these factors were identified between the two groups in multivariate analysis. Although these factors were shown to impact on the prognosis in previous studies, our results suggest that sepsis and severity of infection were lower risk factors for mortality compared with nonoptimal AUC. There was a difference in the age groups between our study and other study,[20–22] we considered that aging had an impact on the prognosis.

**Table 4** Adverse effects of vancomycin among survivors and nonsurvivors

| Adverse effect | Survivors (n = 62) | Nonsurvivors (n = 32) | *P*-value |
|---|---|---|---|
| Nephrotoxicity | 3 (4.8%) | 9 (28%) | 0.003* |
| Liver dysfunction | 3 (4.8%) | 0 (0%) | 0.282 |
| Skin rash | 2 (3.2%) | 1 (3.2%) | 0.718 |

**Notes:** *P*-values were determined by Fisher's Exact test, *$P < 0.01$, survivors versus nonsurvivors. Data are presented as the number of subjects (percentage).

Several studies have examined the relationship between vancomycin treatment outcomes and the in vitro susceptibility of MRSA strains.[23–27] The results of these studies prompted an expert recommendation for administration of higher vancomycin doses with targeted trough levels of 15–20 μg/mL when treating MRSA pneumonia.[13,24] However, the prevalence of MRSA clinical strains with a high vancomycin MIC and whether higher trough concentrations increase the efficacy of vancomycin and/or risk of nephrotoxicity remain uncertain, particularly in the elderly. In the present study, nephrotoxicity attributable to vancomycin was observed in 13 of 94 patients. In nonsurvivors (n = 32), the rate of nephrotoxicity was 28%, whereas that among survivors (n = 62) was only 4.8% ($P = 0.003$, Table 4). We identified a significant difference in the increased nephrotoxicity associated with vancomycin between surviving and nonsurviving patients. In our study, the mortality rate in patients with an AUC >450 μg*h/mL was 73% (11 of 15 patients), and these 11 patients showed inferior renal clearance of vancomycin compared with the 83 patients with an AUC < 450 μg*h/mL ($P = 0.005$, data not shown). This finding indicates that patients with potentially

poor renal function are likely to have increased AUC values and a poor prognosis.

A few limitations of our study warrant mention. First, the number of patients with MRSA pneumonia analyzed in this study was relatively small. Second, the AUC values were not adjusted with the MIC of the MRSA isolates. The relationship between vancomycin treatment outcomes and the in vitro susceptibility of MRSA strains has been examined in several studies, which have demonstrated that clinical failure rates are significantly higher in patients infected by MRSA isolates with a vancomycin MIC of ≥2 μg/mL.[23–25] Further, for the treatment of infections due to MRSA isolates with a vancomycin MIC >1 μg/mL, optimal pharmacodynamic targets may not be achievable using standard vancomycin doses, even though these isolates are reported as susceptible by Clinical Laboratory and Standards Institute standards.[26,27] Therefore, the resulting AUC/MIC ratio would be significantly affected by only small variations in the MIC. During the 6-year period of the present study, all MRSA isolates had a vancomycin MIC ≤ 2 μg/mL, as determined at our institute. Further, in our most recent sampling survey of MRSA (n = 21), the 18 MRSA isolates had a vancomycin MIC of 1 μg/mL (86%), indicating that these isolates had an AUC equal to AUC/MIC (the remaining three isolates showed a vancomycin MIC of 0.5 μg/mL [14%]). Although therapeutic guidelines for vancomycin recommend a target AUC/MIC for vancomycin of >400 μg*h/mL,[10] our present findings suggest that an AUC of 250–450 μg*h/mL is suitable for treatment of MRSA pneumonia with vancomycin in the elderly. As for the reason of this discrepancy, all isolates from study patients were considered to have a vancomycin MIC #1 μg/mL ≤1 μg/mL, and those elderly patients aged 75 years older with potentially poor renal function had increased AUC values and displayed poor prognosis. Notably, all patients who had an AUC < 250 μg*h/mL died, meaning that we have to consider alternative agents rather than vancomycin for elderly patients aged 75 years and older with poor renal function who have difficulty controlling the correct dosage of vancomycin.

## Conclusion

To the authors' knowledge, this is the first study to examine the pharmacokinetics of vancomycin in elderly patients aged 75 years and older with MRSA pneumonia. Our results suggest that an AUC of 250–450 μg*h/mL is a suitable target for initial empiric treatment of MRSA pneumonia in the elderly until the vancomycin MIC is determined. In elderly patients with potentially poor renal function, administration of vancomycin may not be suitable and it may be necessary to consider alternative agents in such cases. We recommend that once the MIC is determined, the dose should be adjusted according to the MIC. We also consider that regular surveillance of the institutional antibiogram (such as vancomycin MIC values) will contribute to optimal use of anti-MRSA agents, including vancomycin, resulting in more effective and safer treatment for elderly patients infected with MRSA.

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## Disclosure

The authors report no conflicts of interest in this work.

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Clinical Interventions in Aging

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ORIGINAL RESEARCH

# The influence of severe hypoalbuminemia on the half-life of vancomycin in elderly patients with methicillin-resistant *Staphylococcus aureus* hospital-acquired pneumonia

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**Background:** Vancomycin (VCM) treatment outcomes depend on the characteristics of the patient, and it is well known that hypoalbuminemia is a risk factor for poor treatment outcomes, as reported in a previous study. However, the reason that severe hypoalbuminemia has an influence on the treatment outcome of VCM remains unknown.

**Objective:** To elucidate the association between severe hypoalbuminemia and VCM treatment outcomes, we examined pharmacokinetic/pharmacodynamic (PK/PD) parameters in elderly patients with severe hypoalbuminemia.

**Methods:** We conducted a retrospective observational study of 94 patients with methicillin-resistant *Staphylococcus aureus* (MRSA) hospital-acquired pneumonia who had been treated with VCM between January 2006 and December 2012. The 94 patients were divided into severe hypoalbuminemia and non-severe hypoalbuminemia groups. The PK/PD parameters and treatment outcomes of VCM were compared between the two groups.

**Results:** The half-life of VCM in the severe hypoalbuminemia group was significantly longer than in the non-severe hypoalbuminemia group (33.2 ± 5.4 vs 24.9 ± 1.6; $P = 0.049$). Area under the concentration curve (AUC)/minimum inhibitory concentration (MIC) values of 250–450 and >450 μg × h/mL were significantly associated with 28-day mortality in the severe hypoalbuminemia group ($P < 0.001$), whereas AUC/MIC values of <250 μg × h/mL were not associated. We also detected a significant difference in the increased percentage of nephrotoxicity in the severe hypoalbuminemia group (6 of 23 patients [26%]) compared with the non-severe hypoalbuminemia group (6 of 71 patients [8%]; $P < 0.001$).

**Conclusion:** These findings indicate that severe hypoalbuminemia influences the half-life of VCM and treatment outcomes in elderly patients (≥75 years of age). To establish a more effective and safer treatment protocol, the issue of malnutrition in elderly patients needs to be addressed and improved.

**Keywords:** methicillin-resistant *Staphylococcus aureus*, elderly patients, vancomycin, severe hypoalbuminemia, pharmacokinetics, pharmacodynamics

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## Introduction

Senior citizens aged 75 years and older represent the largest and most frequent users of health care facilities such as hospitals and long-term skilled nursing and residential homes. Since immune systems are often affected by aging and underlying diseases, incidences of hospital-acquired pneumonia (HAP) induced by methicillin-resistant *Staphylococcus aureus* (MRSA) are more frequent in the elderly.[1] Improving treatment

outcomes for elderly patients with MRSA infections will therefore increase survival and quality of life, and reduce health care expenditure burdens.[2]

MRSA HAP is primarily treated via the intravenous administration of vancomycin (VCM), and the dosage is determined by pharmacokinetic/pharmacodynamic (PK/PD) parameters. However, a previous study involving adult patients with MRSA pneumonia or sepsis failed to show an association between the PK/PD parameters for VCM and treatment outcome.[3] Martin et al[4] recommend a target area under the concentration curve (AUC)/minimum inhibitory concentration (MIC) for VCM of >400 μg × h/mL, while we previously reported that AUC/MIC values of 250–450 μg × h/mL were acceptable for elderly patients.[5] The reason for this discrepancy is currently unclear.

VCM treatment outcomes depend on the characteristics of the patient, and it is well known that hypoalbuminemia is a risk factor for poor treatment outcomes, as reported in a previous study.[6] Hayashi et al[7] reported that hypoalbuminemia was a risk factor with the long-term administration of VCM. However, the reason that hypoalbuminemia has an influence on the treatment outcome of VCM remains unknown.

Since the potency of VCM is dependent on the free unbound form, albumin levels may have an influence on VCM treatment outcomes. In addition, body fluid volume and renal function are frequently decreased in elderly patients, and such patients show large individual differences in PK/PD parameters. Nevertheless, these parameters in elderly patients with hypoalbuminemia have not been clarified. To elucidate the association between severe hypoalbuminemia and VCM treatment outcomes, we examined PK/PD parameters in elderly patients with severe hypoalbuminemia.

## Methods

### Study location and patients

The study was conducted at the National Center for Geriatrics and Gerontology Hospital, Obu, Japan. This 320-bed hospital oversees general (including emergency) services, except pediatrics, and admits approximately 5,000 patients per year (more than 50% of whom are aged over 75 years). The average number of HAP-MRSA patients is 10–20 per year. MRSA is endemic in this hospital, and the ratio of MRSA isolates per total *S. aureus* isolates is approximately 70%.

Over a 7-year period (from January 2006 through December 2012), all hospitalized patients aged 75 years or older with MRSA pneumonia that had been microbiologically confirmed by sputum or blood cultures, and who had been treated with VCM therapy, were identified using the Clinical Pharmacokinetics Department computer database.

### Study design and data collection

We conducted a retrospective observational study with 28-day mortality as the primary outcome for 94 elderly patients with MRSA pneumonia who had been treated with VCM during the 7-year study period. The secondary outcomes were nephrotoxicity and liver dysfunction. The baseline characteristics of the study patients were age, gender, body weight, serum creatinine level, Charlson Comorbidity Index, albumin level, combination antibiotic therapy, diagnosis of pneumonia, and infection severity. In addition, we assessed the relationship between the effect of VCM PK indices, including serum peak and trough concentrations, AUC/MIC values, volume of distribution, half-life, clearance of VCM, single and daily dose of VCM, and dose interval of VCM. The clinical characteristics of the study patients were retrieved from the hospital medical records. For patients with multiple episodes, only the first episode was counted. This study was approved by the Ethics Committee of the National Center for Geriatrics and Gerontology Hospital.

### Definitions

The definition of HAP was based on American Thoracic Society guidelines for the management of adults with hospital-acquired, ventilator-associated, and health care-associated pneumonia.[2] For the purposes of this study, HAP was defined as pneumonia that occurred 48 hours or more after hospitalization for an acute lung infection characterized by a cough, fever, purulent sputum, and an abnormal chest X-ray that was not deemed to be incubating at the time of admission. Among the HAP cases, those with MRSA isolated from blood cultures or sputum that showed no signs of improvement after treatment with broad-spectrum antibiotics, such as carbapenem, for more than 3 days were defined as MRSA HAP.

Severe hypoalbuminemia was defined as a serum albumin level of <2.5 g/dL. The severity rating of pneumonia was defined according to the Japanese Respiratory Society guidelines for the management of HAP[8] and was used to allocate the patients into severe, moderate, and mild groups. The severe group was defined as patients with three or more of the following risk factors or conditions: malignancy or immunocompromized status, impaired consciousness, requiring a fraction of inspired oxygen ($FiO_2$) >35% to maintain a saturated oxygen ($SaO_2$) level >90%, men aged 70 years or older, or women aged 75 years or older, and oliguria or dehydration. The moderate group was defined as patients with

any two of the above risk factors, and in addition, at least one of the following secondary risk factors: C-reactive protein (CRP) ≥20.0 mg/L or extent of infiltration on a chest X-ray (CXR) covering at least two-thirds of one lung. The mild group was defined as all other patients who did not fit the severe or moderate criteria. The patients were divided into a severe hypoalbuminemia and a non-severe hypoalbuminemia group before VCM administration. Nephrotoxicity to VCM was defined as an increase in serum creatinine of 0.5 g/dL or a 50% increase over pretreatment levels.[2] Liver dysfunction was defined according to International Consensus Meeting criteria.[9]

## Pharmacokinetic data

The initial treatment schedule for VCM was simulated to achieve a trough concentration 10–15 μg/mL, with therapeutic drug monitoring (TDM) software using patient characteristics, including age, body weight and serum creatinine (VCM-TDM Microsoft® Excel Version 3.0, Shionogi and Co, Ltd, Osaka, Japan). The serum concentrations of VCM were determined from samples collected during the fifth day from the start of administration. The blood samples were obtained twice: before VCM administration (trough) and 1 hour after VCM administration (peak). The predicted 24-hour AUC values for VCM were calculated using the TDM software based on peak and trough concentrations.

## Statistical analysis

All comparisons were unpaired, and all tests for significance were two-tailed. Continuous variables were compared using the Student's *t*-test for normally distributed variables and the Welch test for non-normally distributed variables. Categorical variables were compared with the chi-square ($\chi^2$) test. In these tests, a two-sided *P*-value of <0.05 was considered to be significant. SPSS version 20.0 software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis.

# Results

The 94 patients were divided into severe hypoalbuminemia (n = 23) and non-severe hypoalbuminemia (n = 71) groups. Demographic data for these groups are summarized in Table 1.

The PK/PD parameters for VCM in the severe hypoalbuminemia and non-severe hypoalbuminemia groups are also summarized in Table 2. Notably, no significant difference was found between the two groups for the mean trough and peak concentrations, clearance of VCM, and whether a single and daily dose of VCM was administered (Table 2). The percentage of AUC values of >450 μg × h/mL in the severe hypoalbuminemia group was significantly higher than in the non-severe hypoalbuminemia group (9 of 23 patients [39%] vs 6 of 71 patients [9%]; $P < 0.001$). The half-life of VCM in the severe hypoalbuminemia group was significantly longer than in the non-severe hypoalbuminemia group (33.2 ± 5.4 hours [15–135] vs 24.9 ± 1.6 hours [10–68]; $P = 0.049$).

AUC/MIC values of 250–450 and >450 μg × h/mL were significantly associated with 28-day mortality as a primary outcome in the severe hypoalbuminemia patients ($P < 0.001$, Figure 1); statistical power was 0.968 and 0.778, respectively. AUC/MIC values of <250 μg × h/mL were not associated ($P = 0.143$, Figure 1).

**Table 1** Characteristics of patients with Methicillin-resistant *Staphylococcus aureus* pneumonia in this study

| Characteristic | Severe hypoalbuminemia (n=23) | Non-severe hypoalbuminemia (n=71) | *P*-value |
|---|---|---|---|
| Age (years) | 82.7 ± 1.4 (75–97) | 82.6 ± 0.7 (75–99) | 0.933[a] |
| Male (%) | 17 (74%) | 46 (65%) | 0.161[b] |
| Body weight (kg) | 41.8 ± 2.2 (28–72) | 43.3 ± 1.1 (27–67) | 0.526[a] |
| Serum creatinine (mg/dL) | 0.8 ± 0.1 (0.2–2.1) | 0.7 ± 0.1 (0.2–2.5) | 0.348[a] |
| Charlson Comorbidity Index | 2.9 ± 0.5 (1–10) | 2.5 ± 0.2 (0–10) | 0.475[a] |
| Albumin (g/dL) | 2.1 ± 0.1 (1.4–2.4) | 3.0 ± 0.1 (2.5–3.6) | <0.001[a] |
| Combination antibiotic therapy | 12 (52%) | 40 (56%) | 0.570[b] |
| Diagnosis | | | |
| Pneumonia/pneumonia and sepsis | 21/2 | 55/16 | 0.143[b] |
| Infection severity | | | |
| Mild | 4 (17%) | 9 (13%) | 0.428[b] |
| Moderate | 3 (13%) | 25 (35%) | <0.001[b] |
| Severe | 16 (70%) | 37 (52%) | 0.009[b] |

**Notes:** Data are presented as the mean ± standard (range) error or the number of subjects (%). [a]*P*-values determined using the Student's *t*-test; [b]*P*-values determined using the $\chi^2$ test.

**Table 2** Vancomycin pharmacokinetic/pharmacodynamic parameters between severe hypoalbuminemia and non-severe hypoalbuminemia patients with methicillin-resistant *Staphylococcus aureus* pneumonia

| PK/PD parameters | Severe hypoalbuminemia (n=23) | Non-severe hypoalbuminemia (n=71) | *P*-value |
|---|---|---|---|
| $C_{max}$ (μg/mL) | 26.8 ± 1.8 (11–44) | 25.7 ± 1.0 (12–40) | 0.606[a] |
| Trough concentration (μg/mL) | 10.9 ± 1.3 (2.7–23) | 9.0 ± 0.7 (1.6–23) | 0.179[a] |
| AUC/MIC (μg × h/mL) | 426.3 ± 43 (150–789) | 340.1 ± 14.0 (167–784) | 0.066[b] |
| <250 (μg × h/mL) | 6 (26%) | 11 (15%) | 0.113[c] |
| 250–450 (μg × h/mL) | 8 (35%) | 54 (76%) | <0.001[c] |
| >450 (μg × h/mL) | 9 (39%) | 6 (9%) | <0.001[c] |
| Vd (L) | 64.0 ± 1.1 (51–71) | 62.3 ± 0.7 (50–95) | 0.223[a] |
| $T_{1/2}$ (hours) | 33.2 ± 5.4 (15–135) | 24.9 ± 1.6 (10–68) | 0.049[a] |
| CLr (mL/minute) | 33.7 ± 3.7 (4.8–58.7) | 40.7 ± 2.1 (7.9–91.2) | 0.101[a] |
| Single dose (mg) | 774 ± 51 (400–1,250) | 815 ± 27 (350–1,250) | 0.456[a] |
| Daily dose (mg/kg/day) | 19.5 ± 1.6 (6.9–34.5) | 20.4 ± 1.2 (3.4–63.1) | 0.658[a] |
| Dose interval (hours) | 25.0 ± 1.7 (12–48) | 26.5 ± 1.5 (12–72) | 0.509[b] |

**Notes:** Data are presented as the mean ± standard error (range) or the number of subjects (%). [a]*P*-values determined using the Student's *t*-test; [b]*P*-values determined using the Welch test; [c]*P*-values determined using the $\chi^2$ test.

**Abbreviations:** AUC, area under the concentration curve; CLr, renal clearance; $C_{max}$, peak concentration; MIC, minimum inhibitory concentration; PD, pharmacodynamic; PK, pharmacokinetic; $T_{1/2}$, half-life of VCM; VCM, vancomycin; Vd, volume of distribution.

We also examined the adverse effects of VCM treatment among the elderly patients and found that 12 of 94 (13%) developed nephrotoxicity after VCM administration. We detected a significant difference in increasing the percentage of nephrotoxicity in the severe hypoalbuminemia group (6 of 23 patients [26%]) compared with the non-severe hypoalbuminemia group (6 of 71 patients [8%]; $P < 0.001$) (Table 3).

In patients with AUC/MIC values of >450 μg × h/mL, the percentage of nephrotoxicity after VCM administration was significantly higher in the severe hypoalbuminemia group than in the non-severe hypoalbuminemia group (67% vs 33%; $P < 0.001$) (Figure 2), whereas the percentage of nephrotoxicity in the non-severe hypoalbuminemia group was significantly higher than in the severe hypoalbuminemia group for AUC/MIC values of <250 μg × h/mL.

## Discussion

This is the first study to have shown that severe hypoalbuminemia influences the half-life of VCM and treatment outcome.

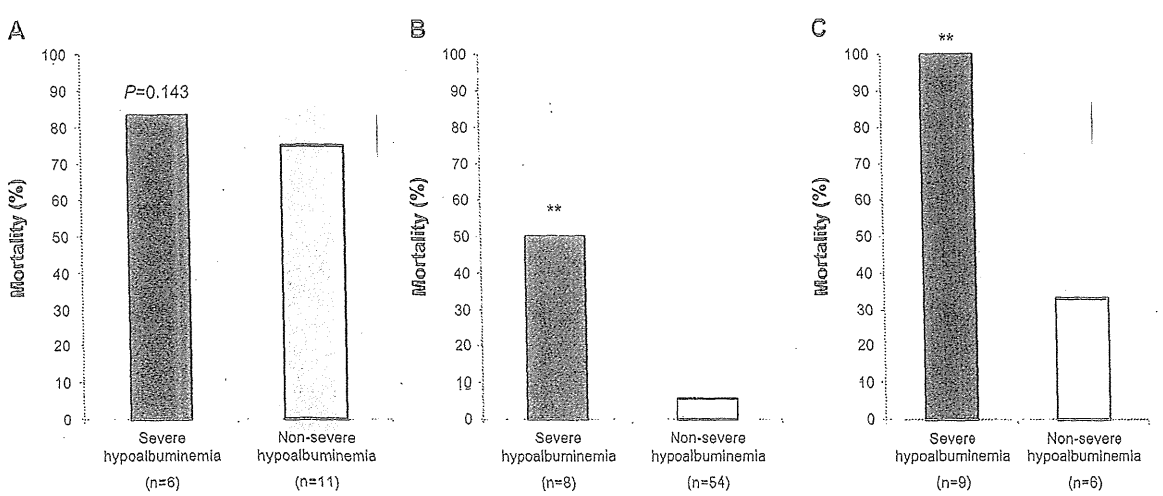


**Figure 1** Twenty-eight-day mortality according to stratification of the vancomycin AUC/MIC values in severe hypoalbuminemia and non-severe hypoalbuminemia groups. (**A**) AUC/MIC <250 μg × h/mL, (**B**) AUC/MIC = 250–450 μg × h/mL, and (**C**) AUC/MIC >450 μg × h/mL. *P*-values were determined using $\chi^2$ tests. The AUC values of 250–450 and >450 μg × h/mL were significantly associated with 28-day mortality in patients with severe hypoalbuminemia (**$P < 0.001$), while AUC values of <250 μg × h/mL were not ($P = 0.143$).

**Abbreviations:** AUC, area under the concentration curve; MIC, minimum inhibitory concentration.

**Table 3** Adverse effects of vancomycin between severe hypoalbuminemia and non-severe hypoalbuminemia patients

| Characteristic | Severe hypoalbuminemia (n=23) | Non-severe hypoalbuminemia (n=71) | *P*-value |
|---|---|---|---|
| Nephrotoxicity | 6 (26%) | 6 (8%) | <0.001 |
| Liver dysfunction | 0 (0%) | 3 (4%) | 0.245 |

**Notes:** Data are presented as the number of subjects (%). *P*-values were determined using the $\chi^2$ test.

Furthermore, patients with severe hypoalbuminemia with AUC/MIC values of >450 μg × h/mL showed evidence of nephrotoxicity.

The volume of distribution and clearance of other highly protein-bound antibacterials, such as teicoplanin, aztreonam, fusidic acid, or daptomycin, were increased in critically ill patients with hypoalbuminaemia.[10] Since the protein-binding rate of VCM is lower than that of teicoplanin,[11] few studies have investigated whether severe hypoalbuminemia influences the PK/PD parameters of VCM in elderly patients. In the present study, the half-life of VCM was longer in elderly patients with severe hypoalbuminemia than in the patients with non-severe hypoalbuminemia. Furthermore, the percentage of AUC/MIC values of >450 μg × h/mL was increased in the patients with severe hypoalbuminemia (Table 2). Although VCM has a relatively low protein-binding rate, these results indicate that severe hypoalbuminemia might affect the concentration of the free form, and prolong the half-life of VCM in elderly patients.

VCM therapeutic guidelines recommend a target AUC/MIC for VCM of >400 μg × h/mL;[3] however, our previous report suggested that AUC/MIC values of 250–450 μg × h/mL were suitable for the treatment of MRSA pneumonia with VCM in elderly patients.[4] The reason for this discrepancy is currently unclear. In the present study, the half-life of VCM was extended in the patients with severe hypoalbuminemia, and the AUC/MIC values of VCM were also higher. Moreover, with an increase in AUC/MIC values, the percentage of nephrotoxicity was also increased in patients with severe hypoalbuminemia (Figure 2). Interestingly, AUC/MIC values of <250 μg × h/mL did not influence 28-day mortality in patients with severe hypoalbuminemia, whereas the mortality rate was high in patients with severe hypoalbuminemia with AUC/MIC values of ≥250 μg × h/mL (Figure 1). These results suggest that elderly patients with severe hypoalbuminemia had a high risk of developing nephrotoxicity and 28-day mortality in the case of target AUC/MIC values of >400 μg × h/mL. Elderly patients with infectious diseases are associated with a high incidence of severe hypoalbuminemia, Moreover, hypoalbuminemia can be acute in severely infected patients, and can be entirely independent

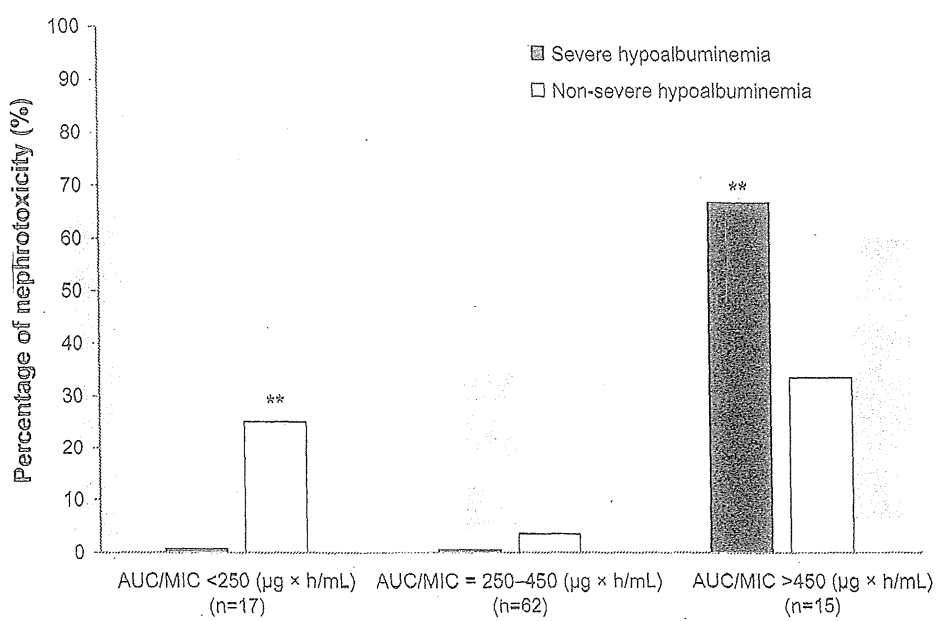


**Figure 2** Percentage of nephrotoxicity after VCM administration in the severe hypoalbuminemia and non-severe hypoalbuminemia groups.
**Notes:** *P*-values were determined using $\chi^2$ tests. The percentage of nephrotoxicity in severe hypoalbuminemia group was significantly higher than that in the non-severe hypoalbuminemia group for AUC/MIC values of >450 μg × h/mL (**$P < 0.001$), whereas the percentage of nephrotoxicity in the non-severe hypoalbuminemia group was significantly higher than in the severe hypoalbuminemia group for AUC/MIC values of <250 μg × h/mL (**$P < 0.001$).
**Abbreviations:** AUC, area under the concentration curve; MIC, minimum inhibitory concentration; VCM, vancomycin.

of baseline nutritional state. Since malnutrition leads to poor outcomes for therapy with VCM, pre-VCM and post-VCM nutrition therapy is important for elderly patients. Although we did not recommend a target AUC/MIC in patients with severe hypoalbuminemia, we consider that elderly patients with low body weight and severe hypoalbuminemia should have their doses individually adjusted by the pharmacist according to those parameters.

A few limitations of our study need to be mentioned here. First, the targeted VCM trough concentration in this study is about 10 μg/mL, which is lower than the guidelines recommended by the Infectious Diseases Society of America/American Society of Health-System Pharmacists: 15–20 μg/mL.[12] Moreover, the average weight of patients in the present study was very low. It was necessary to limit the dosage, because study patients had disuse syndrome or low muscle tone. We consider that elderly patients with low body weight and severe hypoalbuminemia should have their dose individually adjusted by the pharmacist according to those parameters. Second, a relatively small number of patients with MRSA pneumonia were enrolled in this study. Third, this study was retrospective. New, large prospective studies are needed to investigate whether nutritional treatment might be useful for VCM therapy in elderly patients.

## Conclusion

This is the first study to indicate that severe hypoalbuminemia influences the half-life of VCM and VCM-related treatment outcomes in patients aged 75 years or older with MRSA pneumonia. To establish more effective and safer treatments, the issue of nutritional status of elderly patients needs to be addressed.

## Disclosure

The authors reports no conflicts of interest in this work.

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Clinical study

# Location-dependent depth and undermining formation of pressure ulcers

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**KEYWORDS**
Pressure ulcer;
Undermining;
Ulcer location

**Abstract** *Aim of the study:* We examined the location-specific properties of pressure ulcers, focusing on depth and undermining formation, which are often unfavorable factors for ulcer healing.
*Methods:* We conducted a retrospective observational study of 2 independent databases on pressure ulcers. Databases from a 200-bed hospital (database A) and a 300-bed hospital (database B) were collected during different time periods. Relationships between ulcer location, ulcer depth, and undermining formation were analyzed. All pressure ulcers were accurately diagnosed and classified according to their locations.
*Results:* A total of 282 pressure ulcers in 189 patients from database A and 232 pressure ulcers in 154 patients from database B were analyzed. It was found that pressure ulcers primarily developed over the sacrum. Ratio of stages III and IV pressure ulcers was high in pressure ulcers of the foot, ankle, and crus on the lower leg. Among the deep pressure ulcers, undermining formation was frequently observed on the greater trochanter, ilium, and sacrum. In contrast, pressure ulcers of the foot, ankle, and crus did not exhibit undermining formation.

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*Conclusion:* Our results revealed marked differences in pressure ulcer properties depending on their location. Factors affecting depth and undermining of pressure ulcers appear to be related to anatomical and physical properties of the bone and subcutaneous tissue.


## Introduction

A pressure ulcer is localized injury to the skin and/or underlying tissue usually over a bony prominence, as a result of pressure, or pressure in combination with shear [1]. Pressure ulcers are both a medical and a social problem [2–4]. However, reasons for the resistance of deep pressure ulcers to treatment have are not well understood [5,6].

Ulcer location may be related to the specific characteristics of pressure ulcers. The shape of the bony prominence differs according to the pressure ulcer location. Further, physical properties of soft tissue may differ and the direction and magnitude of external forces onto ulcers may depend on the location. Thus, location-specific properties of pressure ulcers may be important for determining prevention and treatment strategies. However, there have been no studies focusing on the relationship between pressure ulcers and ulcer location.

In this study, we aimed to characterize the location-specific properties of pressure ulcers. To examine these properties, all pressure ulcers should be differentiated from other skin diseases such as candidiasis, irritant contact dermatitis, and herpes simplex, as these diseases involve erosion of skin onto a bony prominence. Additionally, a bony prominence should be precisely identified. Therefore, we used 2 independent hospital databases to clarify whether depth and undermining formation are dependent on pressure ulcer location. Retrospective studies have demonstrated clear differences in ulcer depth and undermining formation of pressure ulcers based on location.

## Methods

We conducted a retrospective observational study using 2 independent databases on pressure ulcers. Databases were collected from a 200-bed hospital between December 2001 and June 2004 (database A) and from a 300-bed hospital between January 2011 and August 2012 (database B). All pressure ulcers were routinely diagnosed by board-certified dermatologists at the first medical examination, and their location, depth, undermining formation, size, and presence of infection were recorded. Each pressure ulcer was digitally photographed and was included in the patient medical records. To exclude other skin diseases such as bony prominence lesion, routine dermatological examination including fungal testing and bacterial culture were performed in some cases. A second board-certified dermatologist inspected a photograph of the pressure ulcer to confirm the diagnosis. We excluded 2 ulcers from database A and 3 ulcers from database B that could not be conclusively diagnosed as pressure ulcers.

Depth and undermining formation were determined when necrotic tissues were mostly removed. Ulcer location was determined with respect to the position of the underlying bony prominence. For instance, pressure ulcers at the heel and back developed over the calcaneus and spinous processes, respectively. Other bony prominences corresponding to specific locations are shown in Table 1. Stages of pressure ulcers were determined using the National Pressure Ulcer Advisory Panel (NPUAP) criteria.

Because this was a retrospective study, no interventions for research purposes were made in the diagnosis and treatment of pressure ulcers in these patients.

## Results

### Analyses of pressure ulcers according to location and depth

A total of 282 pressure ulcers in 189 patients from database A and 232 pressure ulcers in 154 patients from database B were analyzed. Database A included patients aged 42–102 years (average, 79.8 ± 11.2 years) and database B included patients aged 41–99 years (average, 80.4 ± 10.9 years). The location distribution of pressure ulcers is shown in Table 1. In database A, 122 (43.3%), 30 (10.6%), and 28 (9.9%) ulcers were located over the sacrum, heel, and greater trochanter, respectively. In database B, the corresponding values were 65 (28%), 32 (13.8%), and 27 (11.6%), respectively. Because pressure ulcer development depends on the external force and the properties of skin and subcutaneous tissues over the bony prominence, the relative ratios of deep pressure

**Table 1** Pressure ulcers from the databases are classified according to the location of bony prominences.

| Location | Bony prominence | Database A ($n$ = 282) | | Database B ($n$ = 232) | |
|---|---|---|---|---|---|
| | | No. | (%) | No. | (%) |
| Sacrum | Sacrum | 122 | (43.3) | 65 | (28.0) |
| Heel | Calcaneus | 30 | (10.6) | 32 | (13.8) |
| Greater trochanter | Greater trochanter | 28 | (9.9) | 27 | (11.6) |
| Coccyx | Coccyx | 24 | (8.5) | 30 | (12.9) |
| Back | Spinous process | 20 | (7.1) | 20 | (8.6) |
| Ilium | Ilium | 12 | (4.3) | 10 | (4.3) |
| Crus | Shaft of tibia and fibula | 11 | (3.9) | 5 | (2.2) |
| Foot | Metatarsals | 7 | (2.5) | 9 | (3.9) |
| Ankle | Lateral malleolus | 4 | (1.4) | 12 | (5.2) |
| Ischium | Ischium | 7 | (2.5) | 5 | (2.2) |
| Shoulder | Acromion include Scapula | 6 | (2.1) | 5 | (2.2) |
| Finger | Phalanges | 3 | (1.1) | 3 | (1.3) |
| Knee | Not identified | 3 | (1.1) | 2 | (0.9) |
| Elbow | Not identified | 2 | (0.7) | 2 | (0.9) |
| Occipital | Skull | 1 | (0.4) | 2 | (0.9) |
| Medial malleolus | Medial malleolus | 2 | (0.7) | 0 | (0.0) |
| Ear | Auricular cartilage | 0 | (0.0) | 2 | (0.9) |
| Arm | Shaft of Radius | 0 | (0.0) | 1 | (0.4) |

ulcers were examined. As shown in Fig. 1, among the 8 major locations, deep pressure ulcers (stages III and IV) were primarily observed on the foot (6/7, 85.7% in database A; 8/9, 88.9% in database B), ankle (3/4, 75.0% in database A; 9/12, 75.0% in database B), and crus (8/11, 72.7% in database A; 3/5, 60.0% in database B).

## Undermining formation is dependent on the ulcer location

Because undermining in pressure ulcers is an unfavorable factor for treatment, the ratio of location-dependent undermining was examined. Undermining formation is principally observed in deep pressure ulcers; thus, the ratio of deep pressure ulcer stages III and IV to each location was examined. Of the major locations, undermining formation was most frequently observed over the greater trochanter (14/16, 87.5% in database A; 10/16, 62.5% in database B), ilium (6/7, 85.7% in database A; 4/6, 66.7% in database B), and sacrum (43/73, 58.9% in database A; 21/32, 65.6% in database B) (Fig. 2). In contrast, undermining formation did not occur on the foot, ankle, or crus, regardless of the frequency of deep pressure ulcers in these areas (Fig. 2).

## Discussion

Studies examining the prevalence of pressure ulcers have provided important information that is applicable to patient care [7–9]. However, previous studies have not examined pressure ulcer location thoroughly. Vanderwee et al. (2007) described the incidence of pressure ulcers at different locations; however, they did not examine the greater

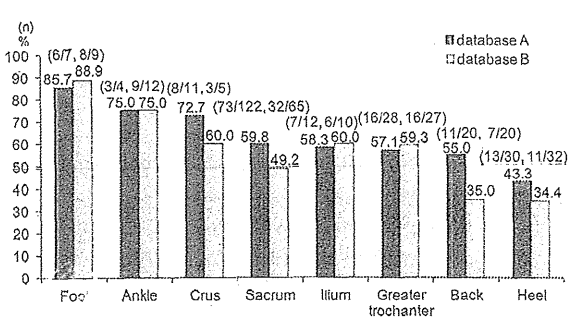


**Figure 1** Ratios of deep pressure ulcers (stages III and IV) according to their location. Ratios of numbers of deep pressure ulcers to all pressure ulcers are indicated.

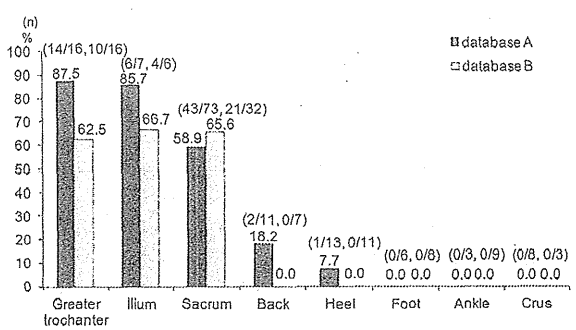


**Figure 2** Ratios of undermining formation according to the location. Ratios of numbers of undermining formation in pressure ulcers to deep pressure ulcers are indicated.

trochanter, coccyx, or ilium [7]. Because pressure ulcers in these locations exhibit specific characteristics, we classified all pressure ulcers in the examined databases according to the bony prominences involved (Table 1). Our results will provide information useful for determining care and treatment for patients with pressure ulcers.

Because the databases used in this study were extracted from 2 sub-urban based hospitals, the number of ulcers examined was small. Moreover, most pressure ulcers in patients developed at the patients' home, where causes cannot be easily identified. However, all pressure ulcers in this study were identified based on their bony prominences. Furthermore, diagnosis of other skin diseases, such as herpes simplex, candidiasis, and contact dermatitis, that often display erosion into bony prominences were excluded. This study was conducted in 2 medium-sized hospitals. Because patients with pressure ulcers are typically elderly and have multiple comorbidities, they are generally admitted to medium-sized hospitals in Japan [10]. Therefore, databases including large numbers of severe pressure ulcer cases with undermining formation can be obtained.

With respect to the location, pressure ulcers were most frequently observed over the sacrum, which is consistent with the findings of previous studies [8,9]. We further clarified the incidence of pressure ulcers at specific locations, such as those over the metatarsal, which was not determined in previous studies [7–9].

Deep pressure ulcer with an undermining formation is the most difficult ulcer to treat. In this study, deep pressure ulcers were primarily observed on the foot, ankle, crus, and over the sacrum, ilium, and greater trochanter. Lahmann and Kottner previously identified a strong relationship between friction forces and superficial skin lesions, as well as between direct compression and deep pressure ulcers [11]. However, external forces on the foot, ankle, and crus are likely to include frictional forces in association with pressure. Therefore, the anatomical properties of bone prominences and subcutaneous tissues appear to influence pressure ulcer depth. Indeed, thickness and physical properties of skin layers differ according to the anatomical site [12–14], which results from varying degrees of wound deformability [15]. Because the NPUAP criteria are determined based on the exposed tissue at the bottom of the ulcer, pressure ulcers located on the thin dermis or subcutaneous tissues may easily reach the lower layers. Additionally, the morphology of the bony prominence may be an important factor affecting pressure ulcer depth because bony prominences of the foot, ankle, and crus are sharper i.e. exhibit a low radius of curvature, than that of the sacrum. Similarly, patient mobility status and body deformity due to contracture of joints may play a major role in pressure ulcer location.

We examined the location-dependent frequency of undermining formation. Pressure ulcers with undermining generally develop over the greater trochanter, ilium, and sacrum. Ohura et al. noted that the development of undermining in pressure ulcers is due to the discharge of liquefied necrosis and external forces [16]. However, in the current study, we did not observe undermining in pressure ulcers located at the foot, ankle, or crus. Because discharge of liquefied necrosis and external forces exist at all locations, anatomical and physical properties of the bony prominence, dermis, and subcutaneous tissue at these locations may prevent undermining formation. In contrast, pressure ulcers over the greater trochanter, ilium, and sacrum are generally undermined. Based on our previous definition concerning wound deformity [15], we identified distinct physical properties of pressure ulcers between the sacrum and foot. Location-specific external force on the ulcer and physical properties of the surrounding tissues may be critical for undermining formation. Future pathological studies examining how these location-specific properties are related to impaired epithelization and contraction, which are observed in undermining pressure ulcers, are required.

In conclusion, this observational study suggests different etiologies of pressure ulcers depending on their locations. Based on our data, we suggest that ulcer location in patients with pressure ulcers should be carefully examined and considered.

## Conflict of interest

None.

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

# Relationship between small cerebral white matter lesions and cognitive function in patients with Alzheimer's disease and amnestic mild cognitive impairment

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**Aim:** The main purpose of the present study was to investigate the influence of small cerebral white matter lesions on cognitive functions, and its difference by clinical stage.

**Methods:** A total of 160 patients with Alzheimer's disease and 40 older adults with amnestic mild cognitive impairment were enrolled in the present study. The Fazekas rating scale was used for the semi-quantitative measurement of white matter lesions. Participants whose scales were more than grade 2 were excluded. Associations between the degree of small white matter lesions and cognitive functions including memory, verbal fluency, working memory, processing speed, and executive function were examined.

**Results:** We found that small white matter lesions influenced the performances of neuropsychological tests differently between Alzheimer's disease and amnestic mild cognitive impairment. Analysis of covariance showed significant effects of interaction on a test that assessed categorical verbal fluency. In the amnestic mild cognitive impairment group, small periventricular white matter hyperintensities were significantly associated with poor performances in categorical verbal fluency; whereas in the Alzheimer's disease group, such associations were not observed. Deep white matter hyperintensities did not influence any cognitive functions examined in both groups.

**Conclusions:** The results suggested the involvement of periventricular small white matter lesions on impairment in verbal fluency, and such influence might be different depending on an individual's clinical stage. Geriatr Gerontol Int 2013; ○○: ○○–○○.

**Keywords:** Alzheimer's disease, cognitive function, mild cognitive impairment, verbal fluency, white matter lesions.

## Introduction

Cerebral white matter lesions (WML) are identified as white matter hyperintensities, areas with high signal intensities on T2-weighed magnetic resonance imaging (MRI). The pathogenesis of WML has not been fully clarified, and the clinical relevance of WML also remains ambiguous. Several histopathological correlates have been reported: enlarged WML including myelin pallor, tissue rarefaction associated with loss of myelin and axons, and mild gliosis.[1,2] The occurrence of WML has been shown to increase with advancing age,[3,4] and the progression of WML has been associated with vascular risk factors.[5] In a meta-analysis, WML predicted an increased risk of stroke, dementia and death.[6]

In some non-demented population-based studies, WML predicted a higher rate of cognitive decline,[4,7–10] especially when located in the periventricular regions.[11–14] In some studies of Alzheimer's disease (AD) patients, it has been suggested that AD patients with WML had worse cognitive performances than those without WML,[15–17] whereas other studies did not find any association between WML and cognitive decline in AD patients.[18,19] Diversities in study samples with varying clinical stages or different methods for the assessment of WML might explain the inconsistent results in those studies. Several studies have suggested that WML could influence cognitive performance in the

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