



Original Article

Clinical Characteristics and Risk Factors for Mortality in Patients with Meningitis Caused by *Staphylococcus aureus* and Vancomycin Minimal Inhibitory Concentrations Against These Isolates

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BACKGROUND/PURPOSE: Bacterial meningitis caused by *Staphylococcus aureus* is uncommon but has a high mortality rate. The aims of this study were to better understand the clinical manifestations of *S. aureus* meningitis, to identify the risk factors for mortality in the affected patients, and to determine the levels of vancomycin minimal inhibitory concentrations (MICs) against these pathogens.

METHODS: A retrospective study of patients with *S. aureus* meningitis hospitalized between December 2000 and December 2008 was made, and vancomycin MICs against *S. aureus* isolates was determined using Etest.

RESULTS: Among 37 patients with *S. aureus* meningitis, fever was most commonly observed. Twenty-six patients (70.3%) had received prior neurosurgery, and 24 (64.9%) patients were suffering from methicillin-resistant *S. aureus* (MRSA) infections. The vancomycin MIC of 2 µg/mL was found in 23 (74.2%) of 31 *S. aureus* isolates available for testing. Excluding three patients who did not receive antibiotics for their *S. aureus* meningitis the mortality rate was 35.3% in the 34 remaining patients, with concurrent infective endocarditis an independent risk factor for mortality (odds ratio=21.00; 95% confidence interval, 1.834–240.515; $p=0.01$).

CONCLUSION: Patients with *S. aureus* meningitis and concurrent infective endocarditis were at a higher risk of mortality. A vancomycin MIC of 2 µg/mL against a substantial number of *S. aureus* isolates that grew from the cerebrospinal fluid suggests the importance of obtaining trough vancomycin concentrations of 15–20 µg/mL for the treatment of MRSA meningitis.

KEYWORDS: bacterial meningitis, infective endocarditis, minimal inhibitory concentration, *Staphylococcus aureus*, vancomycin

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Introduction

Bacterial meningitis caused by *Staphylococcus aureus* is uncommon,^{1–3} yet results in high mortality in affected patients.³ It is also worth noting that patients with methicillin-resistant *S. aureus* (MRSA) bacteremia were reported to have a higher mortality rate and longer hospital stays than those with methicillin-sensitive *S. aureus* (MSSA) bacteremia.⁴ Increasing incidence of MRSA meningitis has been observed among all *S. aureus* meningitis cases.^{1,3} Despite the fact that vancomycin is conventionally the drug of choice for MRSA meningitis, the poor penetration of vancomycin into cerebrospinal fluid (CSF) makes treatment of *S. aureus* meningitis difficult.^{5–7} This is especially true when the minimal inhibitory concentration (MIC) of vancomycin against a *S. aureus* isolate is approaching the *in vitro* susceptible breakpoint of $\leq 2 \mu\text{g/mL}$.^{8,9} The rarity of *S. aureus* meningitis limits the widespread clinicians' awareness of this infection entity. The aims of this study were to better understand the clinical manifestations of *S. aureus* meningitis, to identify the risk factor(s) for mortality in affected patients, and to determine vancomycin MICs against this pathogen.

Methods

Study design, hospital setting and patient population

We carried out a retrospective study of patients admitted between December 2000 and December 2008 at Chang Gung Memorial Hospital, Kaohsiung (a 2,500 bed facility serving as a primary care and tertiary referral center in southern Taiwan). The included patients were found in a database of the hospital's clinical microbiology laboratory. Diagnoses of meningitis in these patients were based on compatible clinical pictures (fever, headache and/or any meningeal signs), laboratory data (pleocytosis in CSF), and the pure growth of *S. aureus* in CSF culture with or without additional *S. aureus* isolated from blood culture. The medical charts of the included patients were reviewed and demographics, clinical and laboratory information were collected.

Antimicrobial susceptibility testing

S. aureus isolates were identified by conventional methods on a clinical service basis.¹⁰ MRSA referred to a *S. aureus* isolate in which the inhibitory zone for ceftioxin was ≤ 19 mm

by the disk diffusion test; any *S. aureus* isolate with an inhibitory zone greater than 19 mm for ceftioxin was regarded as a MSSA.^{10,11} To obtain the vancomycin MIC, all *S. aureus* isolates were subjected to the Etest in accordance with the manufacturer's instructions (AB Biodisk, Solna, Sweden). Briefly, each *S. aureus* isolate was subcultured on a trypticase soy agar plate supplemented with 5% sheep blood, which was then incubated overnight (18–24 hours) at 35°C in ambient air. Subcultured *S. aureus* isolates were inoculated into trypticase soy broth, which was adjusted with 0.9% saline to obtain a turbidity comparable to 0.5 McFarland Nephelometer standards. The standardized suspension was spread onto the surface of a Mueller-Hinton agar plate, which was then allowed to dry for 15 minutes before placement of a vancomycin Etest strip. The MIC of vancomycin was defined as the intercept of the zone of inhibition with the graded Etest strip, which was rounded up to the next highest two-fold dilution when necessary. *S. aureus* ATCC29213 was used as the control strain during susceptibility testing. If the vancomycin MIC was $\leq 2 \mu\text{g/mL}$, the tested *S. aureus* isolate was defined as a vancomycin-susceptible isolate.¹²

Definition

Meningitis was defined as nosocomially acquired if it occurred during the patient's hospitalization or was diagnosed upon his or her admission if the patient had been released from any healthcare facility less than 1 week before.^{2,13} Diabetes mellitus was defined in patients who met at least one the following criteria: (1) random plasma glucose level greater than 200 mg/dL; (2) fasting plasma glucose level greater than 105 mg/dL at recovery from sepsis; and (3) being previously diagnosed as a diabetic and taking an oral hypoglycemia agent or receiving insulin injections. Chronic kidney disease was defined as serum creatinine greater than 2.0 mg/dL or end-stage renal disease subject to regular hemodialysis or peritoneal dialysis. Endocarditis was defined in patients with concurrent *S. aureus* bacteremia and one or more of the following characteristics: surgical or autopsy findings consistent with endocarditis, echocardiographic evidence of valvular vegetation, and the presence of embolic phenomena.¹⁴ Effective empirical antimicrobial therapy referred to treatment with empirically prescribed antibiotic(s) to which the isolated bacteria was susceptible *in vitro*. Suboptimal antimicrobial therapy referred to treatment

of MSSA meningitis with vancomycin instead of oxacillin,^{15,16} or with underdosing of the *in vitro* susceptible antibiotics. The evaluated endpoints were all-cause in-hospital mortality.

Statistical analysis

Patients were divided into deceased and surviving groups. By univariate analysis, comparison of contingency data between the two groups was carried out using a χ^2 test or Fisher's exact test, while comparison of continuous data was performed using Student's *t* test or Mann-Whitney *U* test. A *p* value <0.1 in univariate analyses was entered into a multiple logistic regression model to identify independent risk factors for in-hospital mortality of patients with *S. aureus* meningitis. Variables with a two-tailed *p* value <0.05 were considered statistically significant. All analyses were performed using the SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Clinical characteristics

Thirty-seven cases (6.5%) of *S. aureus* meningitis were identified among 573 cases of bacterial meningitis in Chang Gung Memorial Hospital during the study period. The male/female ratio was 3.625 (29/8), and median age was 43.4 years (range, 0–86 years). The demographic and clinical information for these patients is summarized in Table 1. We found a variety of underlying diseases/conditions among these patients; these included chronic kidney disease (16.2%), malignancies (24.3%), diabetes mellitus (5.4%), concurrent infective endocarditis (18.9%) and intravenous drug use (13.5%). Of the *S. aureus* meningitis cases, 29 (78.4%) were nosocomially acquired and 26 cases (70.3%) had received prior neurosurgery. Fever, the most commonly encountered presentation, was found in 27 (73%) patients. Among the 28 patients whose blood culture was available, *S. aureus* bacteremia was found in only 10 cases (35.7%).

Of the subgroup of seven patients with infective endocarditis, six were male. Fever (5/7) and consciousness change (6/7) were the most frequent clinical presentations and most of the infections were community acquired (6/7). The mortality rate in patients with concurrent infective endocarditis (6/7 fatal) was higher than those without. Among these seven patients, five were intravenous drug

Table 1. Demographic characteristics and clinical outcomes of 37 patients with *Staphylococcus aureus* meningitis

Variable	<i>n</i> (%) ^a
Age (yr)	43.4 (0–86)
Sex, male	29 (78.4)
Clinical manifestations	
Fever	27 (73.0)
Altered consciousness	18 (48.6)
Seizure	2 (5.4)
CSF leakage	7 (18.9)
Shock	5 (13.5)
Concurrent bacteremia	10 (35.7) ^b
Infective endocarditis	7 (18.9)
Underlying diseases/conditions	
Chronic kidney disease	6 (16.2)
Malignancies	9 (24.3)
Diabetes mellitus	2 (5.4)
Intravenous drug use	5 (13.5)
Post-neurosurgery	26 (70.3)
Nosocomial-acquisition	29 (78.4)
MRSA meningitis	24 (64.9)
In-hospital mortality ^c	14 (37.8)

^aData presented as median (range) or *n* (%), one patient may have more than one clinical manifestation and underlying disease/condition; ^bblood culture data only available for 28 patients; ^cincludes three patients that did not receive antibiotics aimed at meningitis, and who were not eligible for assessment of risk factor for in hospital-mortality (see text for details). CSF=cerebrospinal fluid; MRSA=methicillin-resistant *Staphylococcus aureus*.

users, one had end-stage renal disease and another had chronic osteomyelitis. MRSA isolates were found in four cases, except the three intravenous drug user cases, and for three of these MRSA isolates, the vancomycin MICs (2 µg/mL) were high.

Microbiological characteristics

The 37 *S. aureus* isolates were universally susceptible to vancomycin, and 24 (64.9%) of them were resistant to methicillin. Compared with the 31 *S. aureus* isolates that survived preservation, a vancomycin MIC of 2 µg/mL was found in 23 (74.2%) isolates, 1 µg/mL in 7 (22.6%), and 0.5 µg/mL in 1 (3.2%). The annual distribution of the MIC for vancomycin of 2 µg/mL against the *S. aureus* isolates in the years between 2002 and 2008 is shown in the Figure.

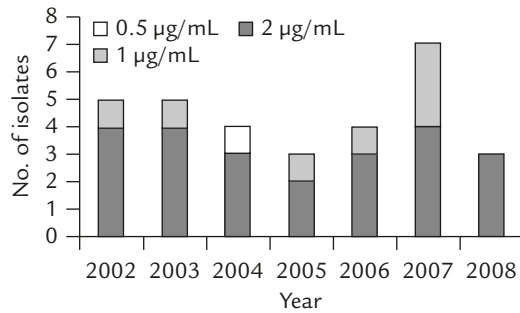


Figure. Annual distribution of vancomycin minimum inhibitory concentrations from 2002 to 2008.

Treatment and prognosis

Three of the 37 patients included in the study did not receive antibiotics aimed at *S. aureus* meningitis during hospitalization because of either poor clinical status (head trauma and in a vegetative status) or delayed diagnosis. These three patients were excluded from assessment of risk factors for in-hospital mortality. Among the 34 assessable patients, 18 (52.9%) received effective empirical treatment, while 24 (70.6%) received suboptimal antimicrobial treatment. Twelve patients died, giving an overall mortality rate of 35.3%. Univariate analyses disclosed that when compared with the surviving group, patients in the deceased group had significantly higher proportions of septic shock (33.3% *vs.* 0%; $p=0.01$), chronic kidney disease (41.7% *vs.* 4.5%; $p=0.01$), intravenous drug use (33.3% *vs.* 4.5%; $p=0.04$), and concurrent infective endocarditis (50.0% *vs.* 4.5%; $p<0.01$) (Table 2). A significantly lower proportion of patients that were post-neurosurgery were found in the deceased group (41.7% *vs.* 81.8%; $p=0.03$) when compared with the surviving group (Table 2). Logistic regression indicated that only concurrent infective endocarditis (odds ratio=21.00; 95% confidence interval, 1.834–240.515; $p=0.01$) was an independent risk factor for in-hospital mortality in patients with *S. aureus* meningitis.

Discussion

The incidence of *S. aureus* meningitis in our study was similar to a previously published series of 19 patients admitted to our hospital between 1986 and 2000.¹ We found similarities in age, sex, post-neurosurgery, proportions of MRSA meningitis, nosocomial acquisition rate and mortality rate, but lower proportions of fever, altered consciousness and seizure at diagnosis of *S. aureus* meningitis (Table 3). These

data suggested an earlier diagnosis of *S. aureus* meningitis before full development of symptoms and signs of infection of the central nervous system in patients in our series. However, the previous data¹ and our current data indicate no improvement in patients with *S. aureus* meningitis in our hospital over the past 22 years in terms of survival.

Nearly 70% of our patients developed *S. aureus* meningitis after neurosurgery, which was comparable to figures in other studies ranging from 43% to 80%.^{3,17–20} The 37.8% (14/37 patients) in-hospital mortality of our patients was comparable to those previously reported, which ranged between 14–77%.^{2–3,17–22} The variability in mortality might result from the differences in clinical severity and underlying diseases/conditions between patients in different series.

The mortality rate in patients with hematogenous *S. aureus* meningitis was reported to be higher than that in patients with post-operative *S. aureus* meningitis (19–71% *vs.* 11–28%).^{17–23} Of note, the in-hospital mortality rate in patients with *S. aureus* meningitis and concurrent infective endocarditis in this series was found to be as high as 85.7% (6/7 patients). One recent report revealed that the mortality rate significantly increased in patients with endocarditis who became infected with *S. aureus* once neurological signs clinically developed.²⁴ Our data, together with those from previous reports²⁵ indicated the existence of endocarditis in approximately 15% of *S. aureus* bacteremic patients, underscoring the importance of a diligent search for possible endocarditis in *S. aureus* bacteremic patients because the likelihood of fatality in patients with *S. aureus* meningitis is high if there is a coexisting endocarditis.

Of the six patients with chronic kidney disease in this series, four of the five deceased patients were infected with a MRSA (Table 2). Adjusting for renal function to avoid toxicity, vancomycin at a dose of 1 g per 24 hours or 1 g per 72 hours was prescribed in our cases, resulting in a trough serum vancomycin concentration below 15 µg/mL, leading to treatment failure,²⁶ as a trough serum vancomycin concentration of 15–20 µg/mL is recommended for treatment of MRSA meningitis.²⁷ In patients with normal renal function (creatinine clearance 70–100 mL/min) and *S. aureus* with low vancomycin MIC (< 1 µg/mL), conventional dosing (loading with 25–30 mg/kg followed by 15–20 mg/kg q8–12 h) renders a sufficient target therapeutic level (area under concentration curve/MIC > 400) in patients with infections including meningitis. However, there is no consensus

Table 2. Comparisons of demographic and clinical data between the deceased and surviving groups of patients with *Staphylococcus aureus* meningitis^a

Variable	Deceased group (n=12)	Survived group (n=22)	p
Age, mean (yr)	40.4	43.6	0.74
Sex, male	9 (75.0)	17 (77.3)	1.00
Clinical manifestation			
Fever	7 (58.3)	17 (77.3)	0.27
Altered consciousness	7 (58.3)	9 (40.9)	0.48
Seizure	0 (0)	2 (9.1)	0.53
Shock	4 (33.3)	0 (0)	0.01
CSF leakage	0 (0)	5 (22.7)	0.14
Concurrent bacteremia, A/B (%) ^b	7/12 (58.3)	3/15 (20.0)	0.06
Infective endocarditis	6 (50.0)	1 (4.5)	<0.01
Underlying disease/condition			
Diabetes mellitus	2 (16.7)	0 (0)	0.12
Chronic kidney disease	5 (41.7)	1 (4.5)	0.01
Malignancy	2 (16.7)	6 (27.3)	0.68
Intravenous drug abuser	4 (33.3)	1 (4.5)	0.04
Post-neurosurgery	5 (41.7)	18 (81.8)	0.03
Nosocomial-acquisition	7 (58.3)	19 (86.4)	0.10
MRSA meningitis	7 (58.3)	14 (63.6)	1.00
Vancomycin MIC of 2 µg/mL, A/B (%) ^b	9/11 (81.8)	12/18 (66.7)	0.67
Effective empirical treatment	7 (58.3)	11 (50.0)	0.73
Suboptimal treatment	7 (58.3)	17 (77.3)	0.27

^aData presented as mean or n (%). One patient might have more than one clinical manifestation and underlying disease/condition; ^bA/B=number of patients/number of patients with data available. CSF=cerebrospinal fluid; MIC=minimum inhibitory concentration; MRSA=methicillin-resistant *Staphylococcus aureus*.

on vancomycin dosing for patients with chronic kidney disease.²⁷ In this scenario, one might either determine the optimal vancomycin dosing by adjusting the prescribed antibiotic based on the measurement of its serum trough level or use alternative antibiotics such as linezolid for patients with MRSA meningitis.

The penetration of vancomycin into the CSF varies greatly, and CSF:serum vancomycin ratios were reported to range from 0–0.18 in hosts with non-inflamed meninges to 0.36–0.48 in those with an inflamed meninges.²⁶ Despite availability of high serum vancomycin levels, unsatisfactory CSF vancomycin levels leading to clinical and bacteriological ineffectiveness have been previously reported.²⁸ Another study showed that intravenous administration of vancomycin barely reached satisfactory levels (5 µg/mL).²⁹ Given this non-favorable antibiotic penetration level in

CSF, successful treatment with intrathecal/intraventricular vancomycin administration with or without additional intravenous administration of vancomycin for patients with shunt- or infusion pump-related meningitis were previously reported.^{29–32} A variety of recommended vancomycin intrathecal/intraventricular doses was found in the literature. The potential meningeal irritation due to high vancomycin concentration in CSF prevents unlimited intrathecal/intraventricular use of vancomycin.³³ Intraventricular vancomycin at 10 mg per day was reported to be safe and therapeutically efficacious in meningitis patients.^{31,33} However, in cases other than ventriculoperitoneal shunt or extraventricular drainage-related meningitis, the therapeutic effects of intrathecal/intraventricular vancomycin use for meningitis caused by MRSA have not been extensively studied.

Table 3. Comparison of demographic and clinical data between the previous study (1986–2000) and this series (2000–2008) of adults with *Staphylococcus aureus* meningitis^a

Variable	Previous study ^b (n=19)	Current study (n=30)	p
Age (yr) ^a	51	56	0.98
Sex, male	12 (63.2)	25 (83.3)	0.17
Clinical manifestations			
Fever	18 (100)	22 (73.3)	0.02
Altered consciousness	16 (94.1)	18 (60.0)	0.02
Seizure	5 (31.3)	1 (3.3)	0.02
Shock	2 (12.5)	5 (16.7)	1.00
Underlying diseases/conditions			
Diabetes mellitus	10 (52.6)	2 (6.7)	<0.001
Chronic kidney disease	1 (5.3)	6 (20.0)	0.22
Malignancy	2 (10.5)	8 (26.7)	0.28
Infectious endocarditis	1 (5.3)	5 (16.7)	0.38
Intravenous drug abuser	2 (10.5)	7 (23.3)	0.45
Nosocomial-acquisition	13 (68.4)	22 (73.3)	0.75
Post-neurosurgery	11 (57.9)	19 (63.3)	0.77
MRSA meningitis	11 (57.9)	20 (66.7)	0.56
In-hospital mortality	6 (31.6)	11 (36.7)	0.77

^aData presented as median or n (%); ^badapted from Chang WN et al [1]. MRSA=methicillin-resistant *Staphylococcus aureus*.

The higher the vancomycin MIC against MRSA, the more likely the vancomycin treatment is to fail in MRSA bacteremia.^{8,9,34,35} Specifically, the estimated rates for treatment success in patients with MRSA bacteremia was 56% if the vancomycin MIC was ≤ 0.5 $\mu\text{g}/\text{mL}$, and as low as 10% if the vancomycin MIC was ≥ 1 $\mu\text{g}/\text{mL}$.^{8,34} The widespread escalation of MICs in *S. aureus* isolates³⁶ implicates the decreasing success rate in the vancomycin treatment of MRSA bacteremia. Theoretically, an increase in the failure rate for vancomycin treatment of MRSA meningitis can be anticipated. The vancomycin-susceptible breakpoint in the guidelines set out by the Clinical and Laboratory Standards Institute has been altered from 4 $\mu\text{g}/\text{mL}$ down to 2 $\mu\text{g}/\text{mL}$.^{27,37} Current Infectious Diseases Society of America guidelines recommend clinicians consider alternative therapies when the vancomycin MIC is ≥ 2 $\mu\text{g}/\text{mL}$ and the MRSA meningitis patient has normal renal function, as the target

area under concentration curve/MIC is unachievable following conventional vancomycin dosing.²⁷ The high mortality rate in our patients may be due to the high percentage (74.2%) of vancomycin MICs being 2 $\mu\text{g}/\text{mL}$.

Some limitations in this study have to be addressed. First, the sample size was small. Second, being a retrospective study, the clinical severity of each case was unable to be assessed. Third, the vancomycin concentrations in serum and CSF in the affected patients were not measured. Nevertheless, this study shows that concurrent infective endocarditis was a risk factor for mortality in patients with *S. aureus* meningitis, along with a vancomycin MIC of 2 $\mu\text{g}/\text{mL}$ against a substantial number of *S. aureus* isolates from the CSF of affected patients in southern Taiwan. This suggests that the achievement of serum vancomycin concentrations ranging 15–20 $\mu\text{g}/\text{mL}$ is extremely important when treating patients with MRSA meningitis.

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