**Staphylococcus aureus** Meningitis in Adults: A Clinical Comparison of Infections Caused by Methicillin-Resistant and Methicillin-Sensitive Strains


**Abstract**
Background: This study was undertaken to compare the clinical characteristics of adult methicillin-sensitive *Staphylococcus aureus* (MSSA) meningitis and adult methicillin-resistant *S. aureus* (MRSA) meningitis.

Patients and Methods: The clinical characteristics and therapeutic outcomes of 19 adult patients with *S. aureus* meningitis, including eight with MSSA infections and 11 with MRSA infections, were analyzed. A comparison was made between the clinical data of the patients with MSSA infections and those with MRSA infections.

Results: Before the end of 1995, MSSA infection was involved in all the adult patients with *S. aureus* meningitis but thereafter, MRSA infection was involved in 79% of the cases. The clinical characteristics found in patients with MSSA infection included underlying medical disorders (75%), community-acquired infection (75%) and mortality rate (13%). The clinical characteristics found in patients with MRSA infection included post-neurosurgical states (91%), nosocomial infections (100%), men outnumbering women (8 : 3), hydrocephalus (36%) and mortality rate (56%). Comparative study between the patient groups (hematogenous and post-neurosurgical) showed that only the mode of acquisition of infection had statistical significance.

Conclusions: This study showed an increase in MRSA infections in adult *S. aureus* meningitis in recent years. The clinical characteristics of patients with MSSA and MRSA meningitis were different. Community-acquired infection was common in hematogenous *S. aureus* meningitis, while nosocomial infection was common in post-neurosurgical *S. aureus* meningitis. Vancomycin should be considered as one of the drugs of choice for initial therapy of adult bacterial meningitis, especially in post-neurosurgical patients.

Key Words
Adults · MRSA meningitis · MSSA meningitis

**Introduction**
*Staphylococcus aureus* is an uncommon pathogen of acute bacterial meningitis in adults [1, 2] and is usually seen in adult patients with bacteremia, parameningeal infections or post-neurosurgical states [3–5]. In recent years, meningitis caused by *S. aureus* strains resistant to penicillinase-resistant penicillin (methicillin or oxacillin) has increased, presenting a therapeutic challenge in the choice of appropriate antibiotics for initial therapy [6–8]. The clinical characteristics of adult meningitis caused by methicillin-sensitive *S. aureus* (MSSA) and that caused by methicillin-resistant *S. aureus* (MRSA) have rarely been compared in previous reports. Here we report on 19 adult patients with *S. aureus* meningitis and make a clinical comparison of MSSA and MRSA infections.

Patients and Methods
We retrospectively reviewed the microbiological record for CSF, blood cultures and medical records, using preexisting standardized forms, of adult patients with bacterial meningitis admitted to Kaohsiung Chang Gung Memorial Hospital over a period of 15 years (January, 1986 – December, 2000). During this time period 243 cases of culture-proved adult bacterial meningitis were identified. Of these 243 patients, 229 patients were found to have a single pathogen with the other 14 cases involving multiple pathogens. Among the 229 adult meningitis patients with a single pathogen, 19 patients had *S. aureus* meningitis. Of the 14 cases of meningitis
caused by multiple pathogens, four involved _S. aureus_. The clinical characteristics and therapeutic outcomes of the 19 adult meningitis patients with _S. aureus_ infection were analyzed in this study. A definite diagnosis of _S. aureus_ meningitis was confirmed by isolation of _S. aureus_ in one or more CSF cultures; classic clinical evidence such as fever, consciousness disturbance and signs of meningeal irritation; typical CSF findings including at least one of the following: pleocytosis (> 250 leukocytes per µl), increased lactate concentration (> 3.5 mmol/l), decreased glucose ratio (CSF : blood < 0.4) or decreased glucose level (< 2.5 mmol/l) if no simultaneous blood glucose was determined.

Nosocomial meningitis was defined as bacterial infection not present when the patient was admitted to the hospital, clinical evidence of infection no sooner than 48 h after admission, or clinical evidence of meningitis within a short period of time after discharge from the hospital where the patients had received an invasive procedure. Patients who developed meningitis related to head trauma with skull fracture or neurosurgical procedures including spinal tapping were classified as having a post-neurosurgical form. Antibiotic susceptibility was determined by the Kirby-Bauer disc diffusion method (Becton Dickinson, BBL, Mueller-Hinton II agars). PCR for _mecA_ gene detection was also carried out for the strains recovered in the period from 1998–2000 and the MRSA strains were confirmed by positive _mecA_ gene detection. The _mecA_ gene was amplified with the specific primer pairs as described by Kampf et al. [9] and this amplification resulted in a 533-bp DNA fragment for the _mec_ gene. 10 µl of the amplified mixture was analyzed on a 1.5% agarose gel. The gels were stained with ethidium bromide (Sigma Chemical, USA) and visualized with UV light. Colony hybridization with a 32P-labelled probe was performed as described previously [10]. The probe was the 533-bp fragment of the _mecA_ gene purified from the above PCR products and confirmed by direct nucleotide sequencing analysis with an automated Model 377 Sequencer (Applied Biosystems Division, Perkin-Elmer Corp., Norwalk, CT). Blood culture was carried out in all patients with clinical evidence of meningitis and pus culture was performed in patients with focal suppuration.

For comparative study, the 19 patients were divided into two groups (hematogenous, post-neurosurgical) according to the physiopathological mechanism of infection. Data including sex, acquisition of infection, initial clinical manifestations, bacteremia, and antimicrobial therapy for the two patient groups were analyzed by means of Fisher’s exact test. Glucose ratio (CSF : blood), and CSF lactate, total protein, glucose and WBC counts for the two patient groups were compared using the Wilcoxon rank sum test. The age between the two patient groups was compared using the Student’s t-test. All analysis was conducted using SAS (1990) [11]. A p-value < 0.05 was considered statistically significant.

### Results

The clinical and laboratory data of the 19 adult _S. aureus_ meningitis cases are listed in Tables 1 and 2. In Table 1, the patients are listed in chronological order, from 1986 to 2000. Of these 19 patients, eight had MSSA meningitis and 11 had MRSA meningitis. The first case of MRSA meningitis (patient 6) occurred in 1996 and all four cases (patients 16–19) occurring in 2000 were MRSA meningitis. All 11 cases with MRSA meningitis had received prophylactic antibiotics before the development of this infection. Oxacillin was the main prophylactic antibiotic used and the others were penicillin G, gentamycin, cefazolin and pipercillin, with a prophylactic duration of 3 to 5 days. In the MSSA group, there was an equal number of men and women with an average age of 42.3 years; in the MRSA group, the male to female ratio was 8 : 3 with an average age of 59.2 years. Six of the 19 cases (patients 2–5, 10, 15) contracted community-acquired infections and the other 13 contracted nosocomial meningitis.

In two of eight patients with MSSA meningitis, post-neurosurgical state was the underlying condition (patients 1, 14). Underlying medical conditions in the other six included diabetes mellitus (DM), cardiac valve diseases, renal disease and substance abuse. In contrast, except for patient 18, all MRSA meningitis patients had post-neurosurgical states as an underlying condition. Cholecystitis s/p cholecystectomy and DM were the underlying conditions of patient 18, and DM was found in four other MRSA meningitis cases (patients 6, 8, 11, 17). Among these 19 cases, the most common clinical manifestations were fever and consciousness disturbance. Other clinical manifestations included hydrocephalus in four cases of MRSA infection, seizures in two cases of MSSA infection and in three cases of MRSA infection, infectious endocarditis in two cases of MSSA infection, focal suppuration in two cases of MSSA infection, infectious spondylitis in two cases of MSSA infection, septic shock in one case of MSSA infection and in one case of MRSA infection and pyomyositis in one case of MSSA infection.

Positive CSF cultures were found in all 19 cases of _S. aureus_ meningitis. Positive blood cultures were found in six cases (patients 2–5, 10, 15) of MSSA infection and three cases (patients 7, 11, 18) of MRSA infection. Those strains grown from blood cultures had the same antibiotic patterns as those grown from CSF cultures. Pus cultures from patients 4 and 15 also grew _S. aureus_. The multidrug-resistant _S. aureus_ strains cultured from the 11 cases (patients 6–9, 11–13, 16–19) showed a resistance to ampicillin/sulbactam, penicillin G and oxacillin but retained a consistent susceptibility to vancomycin. Some of the resistant strains showed their susceptibility to chloramphenicol and tetracycline. Routine CSF data were incomplete in four cases (patients 1, 2, 6, 13). Their results were glucose ratio 0.12–0.73, glucose 2.1–5.7 mmol/l, protein 0.33–3.63 g/l, lactate 2.2–12.5 mmol/l, and WBC 0.02–3.68 × 10⁹/l in MSSA infections, and glucose ratio 0.14–0.80, glucose 0.84–6.40 mmol/l, protein 0.30–3.63 g/l, lactate 2.43–16.3 mmol/l and WBC 0.003–1.09 × 10⁹/l in MRSA infections. Peripheral leukocytosis was found in all cases of MSSA infection and in eight cases (patients 8, 9, 12, 13, 16–19) of MRSA infection. Leukopenia was found in patient 7.

Except for patient 5, iv oxacillin therapy (5–12 g/day) was given to the patients with MSSA infection for a duration of 12–69 days. Because patient 5 was hypersensitive to oxacillin, she received iv vancomycin therapy (2 g/day) for 26 days. Removal of the ventriculo-peritoneal (V-P) shunt was also performed for patient 14. Of the eight cases of MSSA infection, one patient (patient 5) died and the other seven (patients 1–4, 10, 14, 15) survived. Patients 2 and 10