

# Meningitis due to methicillin-resistant *Staphylococcus aureus* (MRSA): Review of 10 cases

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## Abstract

We evaluated retrospectively, 10 MRSA meningitis cases in our hospital that occurred between January 1999 and June 2004. All were post-neurosurgical and were considered to have hospital-acquired meningitis. Fever, leukocytosis, variable conscious levels were the most common findings. Six patients were treated with regimens including teicoplanin, and four with vancomycin. Mean duration of treatment was  $23.5 \pm 18.8$  days (range, 3–60 days). One patient died. In cases of MRSA meningitis, intravenous vancomycin is the mainstay of therapy. However, six of these 10 patients were successfully treated with regimens including teicoplanin, suggesting that this agent may be an alternative to vancomycin in the therapy of these cases.

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## 1. Introduction

*Staphylococcus aureus* may be found causing nosocomial bacterial meningitis and is associated with a high mortality rate. It is usually associated with neurosurgical interventions, staphylococcal bacteraemia or a parameningeal focus. Methicillin-resistant *S. aureus* (MRSA) has emerged as an important cause of hospital-acquired central nervous system (CNS) infections [1–3]. Although the usual therapeutic choice is vancomycin, there have been a few cases reported that have been treated with intrathecal teicoplanin [4–6].

In this study, we analysed the epidemiology, clinical features, treatment modalities, response to treatment and outcome of 10 cases of MRSA meningitis, treated in our hospital between January 1999 and June 2004.

## 2. Method

This study was performed at the Ege University Hospital, a general teaching hospital with an active neurosurgery ward with 78 beds, 16 of which are in an intensive care unit. We retrospectively evaluated the outcome of patients with culture proven MRSA meningitis between January 1999 and June 2004.

A definite diagnosis of MRSA meningitis was based on the isolation of MRSA in at least one CSF culture. Typical CSF findings included a leucocytosis with a predominance of polymorphonuclear cells, a decreased glucose level, increased protein concentration and classic clinical manifestations of meningitis.

Nosocomial meningitis was defined as bacterial infection not present when the patient was admitted to the hospital or clinical evidence of infection within a short period of time after discharge from the hospital where the patient had received an invasive procedure. Patients developing meningitis after neurosurgical procedures were defined as having post-neurosurgical infection.

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Demographic, clinical and laboratory data, predisposing factors, as well as information on response to treatment and outcome were obtained from each patient's hospital records. CSF samples were obtained by lumbar puncture or percutaneous aspiration of shunt reservoir or puncture of extra ventricular drainage tubing. Samples were routinely centrifuged and the deposit Gram stained. Uncentrifuged samples were analysed for leukocyte count, glucose and protein levels. *S. aureus* isolates were identified using routine microbiological methods. Antibacterial susceptibility tests were performed using the Kirby-Bauer disk diffusion method as described by the National Committee for Clinical Laboratory Standards (NCCLS) [7].

### 3. Results

There were a total of 10 patients, eight males and two females. The mean age was  $34.1 \pm 25.6$  years. Three patients were children. Main demographic findings, underlying diseases, treatment modalities, the antibiotics to which the pathogens were sensitive, morbidity and mortality findings of the patients are summarised in Table 1.

All patients had hospital-acquired meningitis and had undergone neurosurgery. Four patients had shunt infections. Patient 2 had a fracture of the fourth cervical vertebra, post-traffic accident. Patient 5 had a gun shot injury to his head, and his temporal bone had been removed due to osteomyelitis. Patient 4 had recent acute myocardial infarction and stroke and had been operated on for a cerebral haematoma. Three patients had neoplasms, one medullablastoma, one cerebellopontine-angle tumour and one cerebellar pilocytic astrocytoma.

Four patients received prophylactic peri-operative cephalosporins (two cefazolin, one cefuroxime, one ceftriaxone). Another patient received ciprofloxacin and amikacin and another, meropenem given to treat a nosocomial urinary tract infection before being diagnosed with meningitis. In six patients concomitant blood cultures were performed, but only one yielded MRSA and one an *Enterococcus* spp. Patient 7 had nosocomial pneumonia and patient 5, osteomyelitis associated with MRSA, at the time they were diagnosed with meningitis.

All patients had fever. Eight of 10 cases had disturbances in level of consciousness and six patients had neck stiffness. Three cases had convulsions and another two cases had nausea and vomiting. Nine cases had leukocytosis ( $16870 \pm 9077/\mu\text{l}$ , all  $>70\%$  PNL); the patient without a leukocytosis had received chemotherapy for medullablastoma 5 days before the diagnosis of meningitis. The mean leukocyte count in the CSF was  $518 \pm 452/\mu\text{l}$ , protein level was  $489 \pm 410$  mg/dl, glucose level was  $33 \pm 22$  mg/dl. Gram stain showed staphylococci in two patients.

Two patients had mixed infections (patient 5 had MRSA + *Enterococcus* spp.; and patient 1, MRSA + methicillin-resistant coagulase-negative *Staphylococcus*

spp.) whereas eight were infected only with MRSA. All strains were sensitive to teicoplanin and vancomycin, seven strains were sensitive to trimethoprim/sulphamethoxazole, five strains were sensitive to clindamycin and two strains were sensitive to rifampicin.

The mean duration of treatment was  $23.5 \pm 18.8$  days (range, 3–60 days). All drugs were given by the intravenous (IV) route. Two patients were treated with vancomycin alone and four with teicoplanin alone. One patient (patient 1) was treated with vancomycin followed with teicoplanin + meropenem due to tubulointerstitial nephritis. The interstitial nephritis resolved after switching from vancomycin to teicoplanin. One patient (patient 7) was treated with cefazolin. The last two were treated with combined regimens, one with vancomycin + chloramphenicol and one with teicoplanin + chloramphenicol. All patients except patient 7 survived.

The only fatal infection (patient 7) was treated empirically with cefazolin and died during this treatment while awaiting the CSF culture results. However, this patient also had concomitant nosocomial pneumonia associated with MRSA. The treatment of all other cases was successful. Patients 1 and 4 developed hydrocephalus. All patients required re-operation; patients 1 and 4 for hydrocephalus; patients 2 and 5 for wound infection; patients 3, 6, 9 and 10 for shunt removal; patients 7 and 10 for their underlying malignancy and patient 8 for replacement of his deep cerebral stimulation apparatus. Three of the surviving nine patients had varying degrees of neurological sequelae, including vegetative state and poor mental status.

### 4. Discussion

MRSA meningitis is usually associated with neurosurgical operations [1,3], as in the case of our patients. High male preponderance is a known feature of meningitis [1–3].

Previous antibiotic therapy, which six of our patients received, is a well-described risk factor for acquisition of MRSA infection [8]. Many MRSA strains are also resistant to several other antibiotics including all other  $\beta$ -lactam antibiotics, macrolides and lincosamides while usually being highly susceptible only to vancomycin and teicoplanin. In these circumstances, the two glycopeptide agents vancomycin and teicoplanin remain as major choices. Clinical studies of vancomycin in the treatment of MRSA meningitis are limited. Vancomycin does not usually penetrate into the CSF in the absence of inflamed meninges, but when meningitis develops, the penetration can be enhanced to a moderate degree [9]. Several treatment failures have been reported when vancomycin has been used alone intravenously, but many cases have been treated successfully with intrathecal application [10,11]. An additional strategy is combination therapy such as vancomycin + rifampicin which has excellent activity against *S. aureus* with low MICs and excellent CNS penetration [12].

Table 1  
Main demographic findings, underlying diseases, treatment modalities, MRSA sensitivities, morbidity and mortality data of patients

Patient no.	Age	Gender	Underlying condition	Treatment (IV) and duration (days)	Susceptibility of MRSA strain	Morbidity	Result
1	17	Male	Surgery—medullablastoma <sup>a</sup>	Vancomycin, 500 mg (2 × 2) (22 d) afterwards teicoplanin (400 mg, 2 × 1 first day afterwards 1 × 1 + meropenem (3 × 1 g) (7 d)	Van, tec, gen, ery, oflox, rif, tet, clin CNS van, tei, gen, erit, ofx, rif	Hydrocephalus second operation, poor mental status	Cured, lived
2	53	Female	Traffic accident-operation—C4 fracture	Teicoplanin (400 mg, 2 × 1) (12 d)	Van, tec, sxt	Second operation	Cured, lived
3	7	Male	Shunt operation—hydrocephalus	Teicoplanin (2 × 80 mg, 12 d)	Van, tec, ofxl rif	Shunt removal	Cured, lived
4	60	Female	Myocardial infarction, stroke—operation, removal of haematoma	Vancomycin (500 mg 4 × 1) + chloramphenicol (4 × 1 g) (54 d)	Van, tec, cli, sxt	Hydrocephalus second operation, poor mental state	Cured, lived
5	40	Male	Gun shot trauma-removal of the temporal bone-osteomyelitis and meningitis after replacement <sup>b</sup>	Teicoplanin (400 mg 2 × 1) + chloramphenicol (4 × 1 g) (60 d)	Van, tec, sxt <i>Enterococcus</i> sp. (van, tei, pen)	Second operation, vegetative state	Cured, lived
6	2	Male	Shunt operation—hydrocephalus	Vancomycin (50 mg 4 × 1) (28 d)	Van, tec, cli, sxt	Shunt removal	Cured, lived
7	50	Male	Surgery cerebellopontine-angle tumour, nosocomial pneumonia	Cefazolin (3 × 500 mg) (3 d)	Van, tec, cli, sxt	Second operation	Died on the third day of the treatment while awaiting the culture results
8	70	Male	Parkinson-operation to place a deep cerebral stimulation apparatus	Teicoplanin (400 mg 2 × 1) (29 d)	Van, tec, sxt	Second operation	Cured, lived
9	20	Male	Shunt operation—hydrocephalus	Teicoplanin (400 mg, 2 × 1 first day afterwards 1 × 1) (12 d)	Van, tec, sxt, cli	Shunt removal	Cured, lived
10	8	Male	Shunt operation—hydrocephalus developing after pilocytic astrocytoma operation	Vancomycin (380 mg 4 × 1) (16 d)	Van, tec	Shunt removal	Cured, lived

van: vancomycin, tec: teicoplanin, sxt: trimethoprim/sulphamethoxazole, cli: clindamycin, p: penicillin, ofx, ofloxacin, ery: erythromycin, gen: gentamicin, rif: rifampicin.

<sup>a</sup> Mixed infection (MRSA + methicillin-resistant coagulase negative staphylococci-MRCNS).

<sup>b</sup> Mixed infection (MRSA + *Enterococcus* spp.).

There are fewer papers describing the use of teicoplanin in MRSA meningitis than those describing vancomycin use [4–6]. Teicoplanin has favourable pharmacokinetics, including an extremely long half-life. Stahl et al. measured the level of teicoplanin in the CSF of seven patients with bacterial meningitis caused by organisms other than MRSA. After a single intravenous dose of teicoplanin, only one patient developed a level above 0.3 mg/l [13]. These data differs from those obtained from an experimental model of meningitis in the rabbit, in which a continuous infusion of teicoplanin resulted in drug concentrations high enough to allow penetration of the drug to inflamed meninges [14]. In the literature, there are no MRSA meningitis case treated only with IV teicoplanin whereas Kralinsky et al. [4], Cruciani et al. [5], and Venditti et al. [6] treated a total of four cases of MRSA meningitis with intrathecal teicoplanin.

In our study, only four patients were treated with vancomycin which in one case was combined with chloramphenicol. In all cases, vancomycin was bacteriologically and clinically successful but in one of them, interstitial nephritis, a very rare complication related to vancomycin use [15], developed and the treatment was switched to teicoplanin. A total of six patients were treated with regimens that included teicoplanin. In two of these six patients, it was combined with other agents (one with meropenem which was chosen because of a probable coexisting Gram-negative agent, and the other with chloramphenicol, empirically). In patient 1, it was started after vancomycin due to development of interstitial nephritis. In the remaining four cases, it was given alone.

Although we could not measure the level of drugs in CSF and sera, all patients except one survived and their infections were cured microbiologically and clinically. Shunt or device removal may have aided this high cure rate.

Teicoplanin was the major antibiotic used in our series. Why was teicoplanin chosen more than vancomycin? The use of teicoplanin is high in our hospital; overall use of teicoplanin (as daily defined dose) was four times higher than vancomycin between March–October 2002 and 2003 [16]. The active promotional efforts of the company may also be influential; Guldal and Semin reported that promotional gifts affected the drug choice of 43.9% of physicians in Turkey [17].

The only fatal case had received an inappropriate antibiotic, which has been found to be associated with a higher mortality in several studies [18,19]. The reported mortality rate due to MRSA meningitis varies widely [1–3,20]. Our results are low when compared with the previous reported mortality rates [1–3,20]. This may be attributed to the low rate of haematogenous infections in our series, which was connected with higher mortality in a previous study [21].

The high re-operation rate of 100% in our study was in part due to the choice of shunt/device removal + antibiotic therapy for the treatment of shunt/device infections [22]. In addition, three patients with malignancy required surgery for their tumours and patient 5 required replacement of his tem-

poral bone after cure of his meningitis and wound infection. The rate of poor mental status or vegetative state, 33%, is similar to previous reports [1–3].

In conclusion, MRSA meningitis is usually associated with previous neurosurgery, including placement of intracranial devices. Although the diagnosis of MRSA meningitis can only be confirmed by CSF culture, a delay in the recovery of the conscious state and the development of fever after neurosurgical operations should alert the clinicians to the possibility of MRSA meningitis. The main therapeutic option in MRSA meningitis is vancomycin. However, in our four cases (the first reported cases of MRSA meningitis treated with IV teicoplanin, as far as we know), it is revealed that teicoplanin can be an alternative, at least in the salvage therapy of MRSA meningitis. There is no study comparing vancomycin and teicoplanin in MRSA meningitis. Such a study may provide an evidence-based approach to MRSA meningitis therapy.

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