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Case report

# A higher area under the concentration-time curve/minimum inhibitory concentration target as a potential prognostic factor for vancomycin treatment of methicillin-resistant *Staphylococcus aureus* meningitis: A case report

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ABSTRACT

The area under the concentration-time curve (AUC)/minimum inhibitory concentration (MIC) – guided approach is recommended for vancomycin therapeutic drug monitoring in severe methicillin-resistant *Staphylococcus aureus* (MRSA) infection. However, evidence regarding the efficacy of vancomycin AUC-guided strategies for the treatment of systemic infections is limited. This case report describes the successful treatment of MRSA meningitis, with vancomycin using a higher AUC/MIC target. A 61-year-old woman who underwent ventriculoperitoneal (VP) shunt placement for subarachnoid hemorrhage, developed MRSA meningitis due to shunt infection. Vancomycin was administered intravenously, with concurrent monitoring of serum and cerebrospinal fluid (CSF) vancomycin concentrations and AUC/MIC. On post-operative day (POD) 24 of VP shunt placement, the vancomycin trough concentration and AUC/MIC were 12.0 μg/mL and 515, respectively, with persistently positive CSF culture. On POD 28, the trough concentration and AUC/MIC were 18.6 μg/mL and 610, respectively. There were no major adverse events, and CSF culture turned negative on POD 30. The vancomycin CSF-to-serum ratio was approximately 41 %. For patients with MRSA meningitis, we suggest an optimal therapeutic range with a vancomycin AUC/MIC target near the upper limit of the therapeutic window.

## Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a primary cause of cerebrospinal fluid (CSF) shunt infections, with vancomycin acting as the primary antibiotic [1]. The recommended vancomycin trough concentration ranges from 15 to 20 μg/mL under the trough-guided strategy [1]. Notably, therapeutic drug monitoring of vancomycin in severe MRSA infections has transitioned from the

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traditional trough-guided approach to an area under the concentration-time curve (AUC)-guided strategy, with an aim of achieving an AUC/minimum inhibitory concentration (MIC) of 400–600 [2–4]. Although the effectiveness of vancomycin AUC-guided strategies has been demonstrated in MRSA bacteremia and pneumonia, their effectiveness in the treatment of central nervous system (CNS) infections and osteomyelitis is still poorly understood [2–4]. In this report, we present a case illustrating the successful management of methicillin-resistant *Staphylococcus aureus* (MRSA) meningitis resulting from ventriculoperitoneal (VP) shunt infection and treatment with vancomycin using a higher AUC/MIC target.

## Case presentation

A 61-year-old woman (height, 145 cm; weight, 42 kg) was admitted to our intensive care unit after a bilateral frontal craniotomy for subarachnoid hemorrhage in September 2021. On day 24 post-admission, the patient developed hydrocephalus, necessitating the placement of a right VP shunt (post operative day: POD 0). On POD 13, she presented with a fever of 38.8 °C. On POD 17, computed tomography of the head revealed exacerbated hydrocephalus, indicative of a VP shunt infection. As a result, the VP shunt was removed, and a right external ventricular drain (EVD) was inserted. Concurrent CSF sampling and blood cultures were performed. CSF analysis revealed a cell count of 3760/μL (multinucleated cells 91 %), a protein concentration of 243 mg/dL, and glucose level of 9 mg/dL. The patient was diagnosed with healthcare-associated meningitis attributable to a VP shunt infection, prompting initiation of tazobactam/piperacillin. Gram staining of the CSF sample following day revealed gram-positive cocci in clusters, and GeneXpert MRSA/SA BC (Cepheid, USA) confirmed the presence of *mecA* and *spa* genes. Consequently, the antimicrobial regimen was changed to intravenous vancomycin at a dose of 1000 mg (25 mg/kg) every 12 h (Fig. 1). The serum creatinine level on the same day was 0.42 mg/dL. Both blood and CSF cultures showed the growth of MRSA with a vancomycin MIC = 1 μg/mL, identified using MicroScan (Beckman Coulter, USA). Vancomycin concentrations in serum and CSF were quantified using a VANC Flex reagent cartridge (Siemens Healthcare Diagnostics, USA). Peak and trough concentrations of vancomycin were measured one hour after administration and within 30 min after administration, respectively. The vancomycin AUC/MIC was calculated from the peak and trough concentrations using Bayesian estimation software (Practical AUC-Guided TDM for Vancomycin, ver. 2.1) [5]. At the same time, the measured trough and CSF concentrations were used to calculate vancomycin CSF-to-serum ratio.

On POD 22, the right EVD was removed owing to decreased drainage volume and a left EVD was inserted. On POD 24, vancomycin parameters—trough concentration, peak concentration, CSF concentration, and AUC/MIC were 12.0 μg/mL, 23.7 μg/mL, 5.4 μg/mL, and 515, respectively (vancomycin 1000 mg q8hr). The CSF-to-serum ratio was 0.45. The CSF sample had a cell count of 1315/μL (multinucleated cells 70 %), and a protein of 335 mg/dL. The CSF culture remained positive, leading to an increase in vancomycin dose to 1250 mg (30 mg/kg) every 8 h on POD 25 due to persistent MRSA positivity.

Vancomycin trough concentration and AUC/MIC on POD 28 were 18.6 μg/mL and 610, respectively. On the same day, the left EVD was removed because of obstruction, and the right EVD was re-inserted. A repeat CSF culture obtained on POD 30 was negative, and revealed a cell count of 24/μL (multinucleated cells 48 %), and a protein level of 482 mg/dL. Vancomycin trough concentration and AUC/MIC were 16.4 μg/mL and 700, respectively. The CSF vancomycin concentration on POD 32 was 6.2 μg/mL. Therefore, the CSF-to-serum ratio on POD 30 was extrapolated to 0.38. On POD 38, vancomycin dose was reduced to 1000 mg every 8 h due to increased vancomycin trough concentration (21.7 μg/mL) and AUC/MIC (720). On POD 47, vancomycin was discontinued owing to a drug eruption. On POD 51, the CSF cell count was 18/μL (multinucleated cells 96 %). Throughout the treatment period,

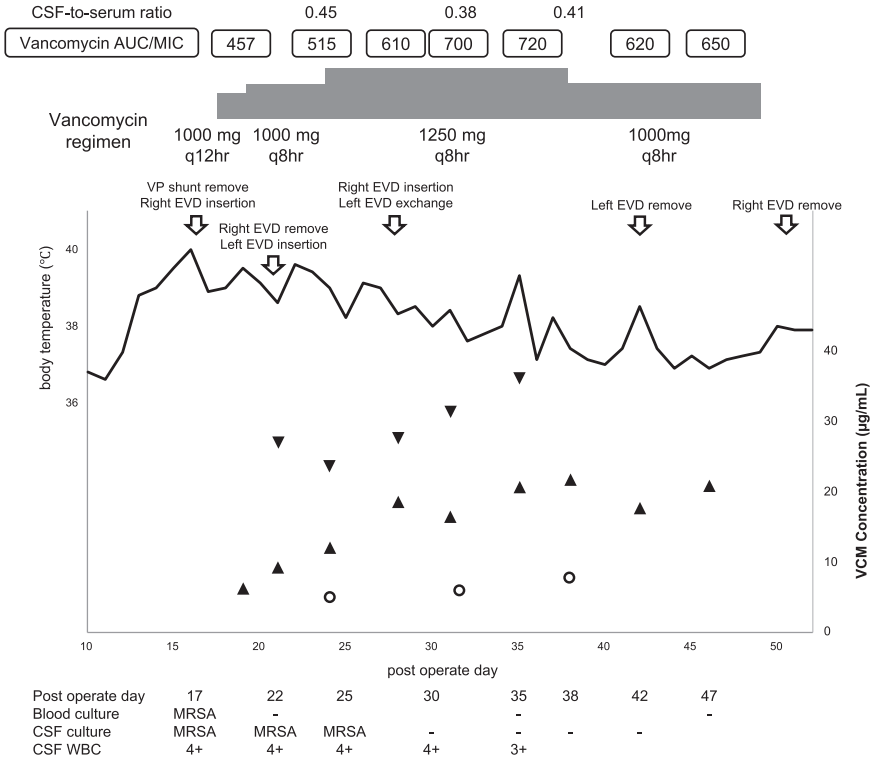


**Fig. 1.** Relationship between clinical and microbiological efficacy and vancomycin concentration in serum and cerebrospinal fluid. The gray shaded areas represent the vancomycin dosing schedule, with dosage visualized by height. The trough concentration in serum is denoted by the closed up-pointing triangle, peak concentration in serum by the closed down-pointing triangle, and concentration in cerebrospinal fluid by the open circle. CSF, cerebrospinal fluid; MRSA, methicillin-resistant Staphylococcus aureus; VP, ventriculoperitoneal; EVD, external ventricular drain.

there were no instances of acute kidney injury [6], brain abscess, or spinal fluid leakage. The mean vancomycin CSF-to-serum ratio was approximately 41 %, and the CSF concentrations of vancomycin were correlated with the trough concentrations and AUC of vancomycin, respectively. No recurrences were observed during the 12-month follow-up period.

## Discussion and conclusions

We report a case of MRSA meningitis that was effectively treated using an increased vancomycin AUC/MIC target strategy. In MRSA meningitis due to VP shunt infection, achieving an AUC/MIC toward the upper limit of the therapeutic window may improve therapeutic outcomes.

This case report indicates that vancomycin may not have bacteriologic activity for MRSA meningitis, even if the AUC/MIC reaches or exceeds 400, which is a conventional target value. Notably, negative blood cultures were confirmed early in the treatment despite achieving an AUC/MIC of $\geq$ 400. However, negative CSF cultures were obtained only after an AUC/MIC near the upper limit of the therapeutic window. In the past, using of vancomycin trough concentrations of 15–20 μg/mL was recommended for MRSA meningitis due to limited tissue penetration [1]. Previous reports showed a moderate correlation between vancomycin trough values and AUC, with patients achieving trough values of 15–20 μg/mL generally exceeding the AUC 400 μg * h/mL. However, a significant 5-fold variation in AUC was observed at a given vancomycin trough value [7,8].

In our case, negative CSF cultures coincided with an AUC/MIC near the upper limit of the therapeutic window. For patients with MRSA-related infective endocarditis, higher trough concentrations (15–20 μg/mL) were recommended, with an AUC/MIC = < 600 identified as a risk factor for treatment failure [9]. Consequently, our experience suggests that an AUC/MIC at or above the upper limit may be optimal for MRSA meningitis patients [2–4]. Emphasizing the importance of source control, continuous monitoring of kidney function is imperative, as vancomycin AUC exceeding 600 μg * h/mL is associated with vancomycin-induced acute kidney injury [10–13]. Meta-analyses have consistently shown that vancomycin AUC-guided strategies significantly reduce the risk of vancomycin-induced kidney injury compared to trough-guided approaches [10,11,13]. Consequently, an AUC-guided strategy has emerged as an alternative method for managing MRSA meningitis.

CSF vancomycin serves as a potential predictor of treatment effectiveness by directly assessing vancomycin levels in infected tissues. If it is possible to measure vancomycin CSF concentrations once, these CSF concentrations may show strong correlations with both vancomycin trough concentrations and AUC in intra-individual variations. At MRSA-positive and MRSA-negative culture points, vancomycin concentrations in the CSF were 5.4 μg/mL and 6.2 μg/mL, respectively. The influence of small fluctuations in CSF vancomycin concentrations on therapeutic efficacy remains unclear as no effective CSF vancomycin concentration range has been established in meningitis [14]. Serum vancomycin trough concentrations and AUC do not correlate with AUC tissue exposure in diabetic patients with limb infection [15]. Previous studies have reported that CSF vancomycin concentrations can be predicted using serum vancomycin trough concentrations adjusted for CSF protein or lactate levels [16–18]. The measured CSF concentrations of vancomycin were essentially equivalent to the free vancomycin concentrations in the CSF, because CSF protein concentrations are typically much lower than plasma protein concentrations. In addition, CSF concentrations showed slight changes compared to the range of peak and trough concentrations in serum [16,19]. Further studies are needed to establish an effective CSF concentration range of vancomycin in meningitis, utilizing serum trough concentrations, serum AUC, CSF-to-serum ratio, plasma and CSF protein levels, and other relevant factors are used to predict CSF concentrations and AUC.

This case report had several limitations. First, the CSF concentration was measured using a serum concentration measurement system, potentially resulting in less precise measurements. Nevertheless, we contend that CSF concentrations exhibited a comparable degree of variability, because they were measured under identical conditions. Second, the VP shunt removed on POD 17 was not cultured. However, subsequent CSF cultures confirmed persistence of MRSA shortly after shunt replacement, thereby confirming the presence of MRSA meningitis.

In conclusion, the use of the AUC-guided strategy for therapeutic monitoring appears promising. If this strategy is adopted as a monitoring parameter, a higher target vancomycin AUC/MIC near the upper limit of the therapeutic window may be appropriate for MRSA meningitis. Further research is imperative to determine the ideal vancomycin AUC/MIC and the concentrations or AUC in CSF for treating MRSA meningitis.

## Ethical approval

The Medical Ethics Committee at St. Marianna University determined that ethical approval was not required for this case report.

## Ethics approval and consent to participate

Since this is a case report, ethical approval was deemed unnecessary by the Medical Ethics Committee at St. Marianna University.

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## CRediT authorship contribution statement

**Yuta Katsuta:** Writing – review & editing, Data curation. **Junpei Tada:** Writing – review & editing, Data curation. **Hiroyuki Kunishima:** Writing – review & editing. **Takashi Matsuzaki:** Writing – review & editing, Supervision. **Kenichi Nakazono:** Writing – original draft, Data curation, Conceptualization. **Hiroki Saito:** Writing – review & editing, Supervision. **Ayaka Ohkubo:** Writing – review & editing, Data curation. **Hidetaka Onodera:** Writing – review & editing. **Haruaki Wakatake:** Writing – review & editing.

## Competing interests

The authors have no conflicts of interest to declare.

## Availability of data and materials

Not applicable.

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### *Consent*

Written informed consent for the personal clinical details of the patient to be published has been obtained by a patient's husband, because the patient's consciousness is not clear due to the disease.

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