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Report

Influence of Empirical Therapy Utilizing Vancomycin in Patients with Suspected Bacterial Meningitis: A Single-Center Retrospective Study

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The incidence rate of bacterial meningitis caused by methicillin-resistant staphylococci is lower than that of bacterial meningitis caused by other gram-positive bacteria. However, considering the high mortality rate of staphylococcal infections, empirical vancomycin (VCM) therapy is often used. On the other hand, VCM is known to affect renal function. Therefore, it is necessary to understand the risks of empirical VCM therapy in patients with suspected bacterial meningitis. We aimed to investigate the risk of acute kidney injury (AKI) associated with empirical VCM therapy in patients with suspected bacterial meningitis. We reviewed the records of 35 suspected bacterial meningitis patients treated with empirical VCM therapy at Fukuoka University Hospital between 2011 and 2017. The incidence rate of AKI associated with empirical VCM therapy was evaluated based on Kidney Disease: Improving Global Outcome criteria. The patients were aged 65.0 (44.0-75.0) years, and had various underlying diseases such as subarachnoid hemorrhage, cerebral hemorrhage, other diseases of the head and community-acquired infection. Methicillin-resistant staphylococci were detected in only 3 patients. In 4 patients with negative culture results, empirical VCM therapy was continued for more than 1 week; this resulted in AKI. The incidence rate of AKI associated with empirical VCM therapy was 11.4%. For patients with suspected bacterial meningitis requiring empirical VCM therapy, it is important to check the necessity of VCM by bacterial culture tests and ensure the safety by monitoring blood concentrations in order to avoid the risk of AKI.

Key words vancomycin, empirical therapy, bacterial meningitis, acute kidney injury, staphylococcus

INTRODUCTION

The prognosis of a patient with bacterial meningitis may depend heavily on the choice of initial treatment. As with other infectious diseases, it is necessary to consider the patient's background, medical history, and disease severity when selecting an appropriate antibacterial drug. In cases of bacterial meningitis, particularly those of nosocomial origins (e.g., cases involving head trauma and neurosurgery patients), the prognosis can worsen rapidly. Empirical therapy, which involves the selection of an antibacterial agent based on experience, is often employed in the early stages of treatment to address the infection as quickly as possible. In such cases, until the causative bacteria are identified, combined therapy with antimicrobial agents against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* is recommended.[1,2] When combination therapy is prescribed, vancomycin (VCM) is recommended as a first-line drug against MRSA.[3] Additionally, VCM often shows antibacterial activity against resistant staphylococci other than MRSA.[1,2] Thus, treatment can be started without waiting for the results of a drug sensitivity test; this is an advantage when staphylococci are identified using rapid tests such as Gram staining. For effectiveness in MRSA meningitis patients, a high blood trough concentration of VCM (15–20 μg/mL) must be maintained.[4] However, this may cause adverse effects such as damage to renal function.

The reported rate of bacterial meningitis caused by *S. aureus* is only 1–9% in Japanese.[2] Therefore, the rates of meningitis caused by MRSA and methicillin-resistant coagulase-negative staphylococci (MR-CNS) are even lower. Thus, many patients may not benefit from empirical VCM therapy but still be at risk of renal dysfunction. However, considering the importance of early treatment for bacterial meningitis, it is difficult to exclude empirical VCM therapy from the potential treatment options for nosocomial bacterial meningitis. For the initial treatment of patients with suspected bacterial meningitis, it is important to prescribe VCM while fully understanding the associated risk. However, empirical therapy with VCM as the first-line drug is only recommended in cases of bacterial meningitis and catheter-related infections.[1,2] Therefore, there is little information regarding the risks associated with empirical VCM therapy.

In this study, we retrospectively investigated the effects of empirical VCM therapy in patients with suspected bacterial meningitis to evaluate its efficacy and associated risks.

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MATERIALS AND METHODS

Study Design and Population Information was extracted from the medical records of 496 patients with suspected bacterial meningitis admitted to Fukuoka University Hospital from January 2011 to December 2017. These patients were suspected of having meningitis and underwent a cerebrospinal fluid culture test. There were 42 patients who required empirical coverage for MRSA. Of these, 35 patients who received VCM as empirical therapy were included in this study (Fig. 1). Bacterial meningitis is common in children; however, because the bacterial strain observed in children differs from that in adults[1,2] and has distinct pharmacokinetics, patients younger than 18 years of age were excluded. Patients who received VCM for <3 d and those who were undergoing dialysis were also excluded.

Survey Items We retrospectively evaluated the diagnosis, age, sex, patient background, medication history, bacterial culture results, and biochemical test results in each case using our electronic medical record system. Antimicrobial susceptibility was evaluated using the broth microdilution method and the disk method. These methods were performed in accordance with the guidelines provided in the Clinical and Laboratory Standard Institute manual.[5]

Acute Kidney Injury Incidence To assess the incidence rate of acute kidney injury (AKI) associated with empirical VCM therapy, we used the Kidney Disease: Improving Global Outcome (KDIGO) diagnostic criteria.[6] AKI was defined as a serum creatinine (SCr) increase of at least 0.3 mg/dL or an increase of at least 1.5-fold from the baseline. The maximum SCr level during the VCM administration period was defined as the evaluation value. The baseline SCr level was the value measured before the initiation of empirical VCM therapy.

Effectiveness Evaluation The clinical efficacy of VCM was evaluated from the date of administration of the first dose to the 4th, 7th, and final days of the administration period. Treatment was considered effective when at least two of the following criteria were satisfied (and exacerbation was not observed with respect to any of the unsatisfied criteria): (1) a body temperature of < 37.0°C (i.e., reduction from fever temperatures), (2) an improvement in the white blood cell (WBC) count to < 8,000/mm^3 or to a standard value, and (3) an improvement in C-reactive protein (CRP) levels to ≤ 30% of the pre-dose value.[7] The bacteriological effect was defined as the disappearance, decrease, bacterial change, or unchanged based on cerebrospinal fluid culture results. Finally, VCM treatment was considered effective when both clinical efficacy and a resultant disappearance of or decrease in the number of detected bacteria were noted. These criteria are based on our previous study of staphylococcal infections.[8]

Ethical Considerations This study was approved by the Ethics Committee on Medicine at Fukuoka University (approval number 18-11-04).

Statistical Analysis We used the Mann-Whitney U test or Fischer's exact test for all between-group comparisons. The Wilcoxon signed-rank sum test was used to compare the baseline SCr level to the maximum observed SCr level. Data are presented as medians (interquartile ranges). In all analyses, a P value of < 0.05 was defined as statistically significant. All analyses were performed using JMP®, ver. 12.0.1 (SAS Institute, Tokyo, Japan).

RESULTS

Patient Demographics The background characteristics of the study patients are shown in Table 1. Thirty-three of the 35 patients had underlying neurological diseases and were undergoing drainage. Therefore, most patients who were prescribed empirical VCM treatment had suspected nosocomial bacterial meningitis due to the use of a device such as an external ventricular drain.

Figure 2 shows the VCM administration period. In total, 17 patients (3 d, 8 cases; 4–6 d, 9 cases) were treated with VCM for less than 1 week. In 8 patients, the treatment period was as short as 3 d; in these patients, treatment was terminated because Gram staining revealed no gram-positive bacteria. For the 9 patients who received VCM for 4–6 d, VCM administration was stopped based on cerebrospinal fluid culture results. Resistant staphylococci such as MRSA were not detected in any patient who received VCM for less than 1 week. In con-

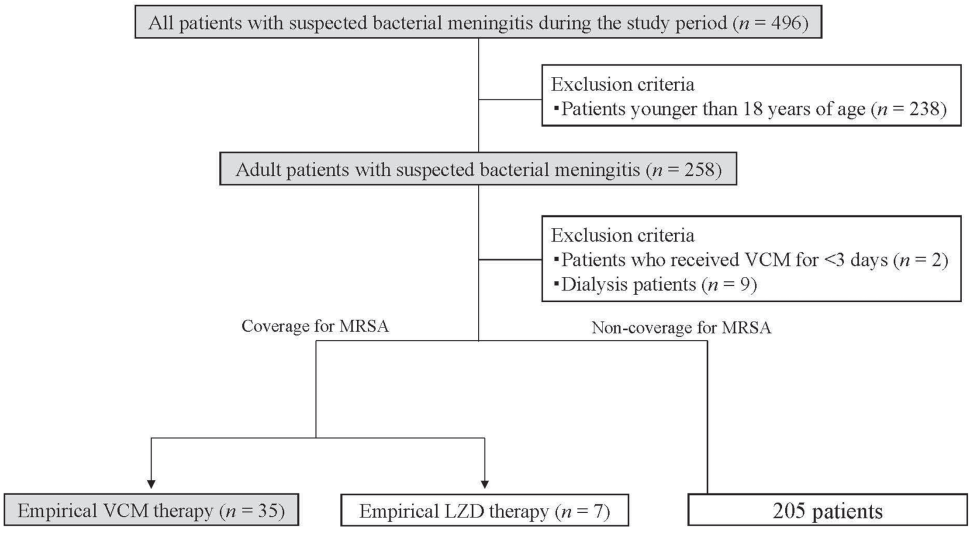

Fig. 1. Flowchart Depicting the Selection of Target Patients in This Study

VCM: vancomycin, LZD: linezolid, MRSA: methicillin-resistant *Staphylococcus aureus*

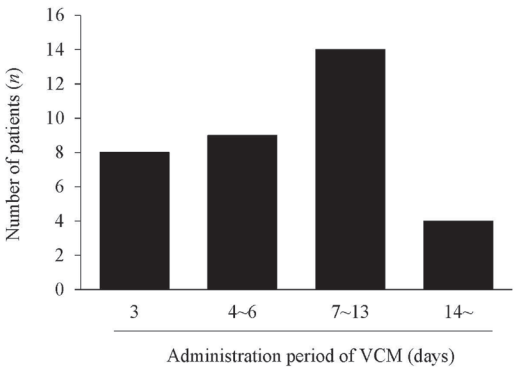

Fig. 2. Administration Period of Vancomycin (VCM)

VCM: vancomycin

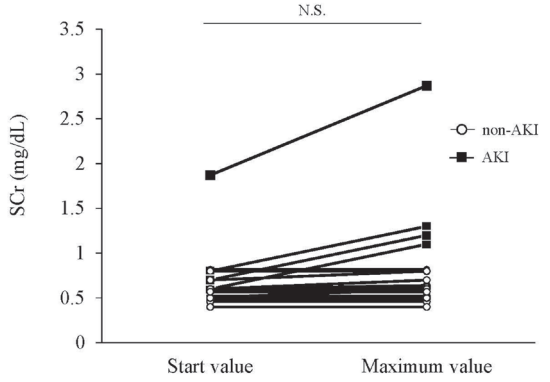

Fig. 3. Effects of VCM on Serum Creatinine Levels

Black squares indicate patients with AKI; white pills indicate patients without AKI. AKI: acute kidney injury, SCr: serum creatinine, N.S.: not significant

Table 1. Characteristics of the Patients Included in This Study

	VCM (n = 35)
Male / female	17 / 18
Age (years)	65.0 (44.0 – 75.0)
Underlying disease (n (%))	
Subarachnoid hemorrhage*	17 (48.6%)
Intracerebral hemorrhage	11 (31.4%)
Other head diseases	5 (14.3%)
Community-acquired infection	2 (5.7%)
Laboratory data	
BT (℃)	38.1 (37.8 – 38.9)
WBC ($\times 10^3$ /μL)	14.9 (10.8 – 17.5)
CRP (mg/dL)	5.8 (3.1 – 12.3)
SCr (mg/dL)	0.6 (0.5 – 0.8)
Concomitant antimicrobial agent (n (%))	
MEPM	16 (45.7%)
CTRX	9 (25.7%)
ABPC/SBT	6 (17.1%)
CFPM	5 (14.2%)
PZFX	1 (2.9%)
Nothing	3 (8.6%)

* Including traumatic subarachnoid hemorrhage. VCM: vancomycin, BT: body temperature, WBC: white blood cell, CRP: C-reactive protein, SCr: serum creatinine, MEPM: meropenem, CTRX: ceftriaxone, SBT/ABPC: sulbactam/ampicillin, CFPM: cefepime, PZFX: pazufloxacin. Values are presented as numbers (%) or medians (interquartile ranges).

trast, among the 18 patients who received VCM for 1 week or longer (7–13 d, 14 cases; ≥ 14 d, 4 cases), 3 had meningitis caused by methicillin-resistant staphylococci. Methicillin-resistant staphylococci were not detected in the remaining 15 patients, but they were still treated with VCM for more than 1 week.

Frequency of AKI Associated with Empirical VCM Therapy Figure 3 shows the patients' baseline SCr levels and the maximum SCr levels during the VCM administration period. In all cases, no significant increase in SCr levels was observed during the VCM administration period. However, the incidence rate of AKI associated with empirical VCM therapy was 11.4% (4 of 35 cases). Table 2 shows detailed information on these cases (Cases 1–4). No cases deviated significantly from the recommended dose (15–20 mg/kg/time) in the Japanese TDM guidelines.[4] Blood trough levels of VCM were measured only in Cases 1 and 2. In both cases, the blood trough concentration did not exceed 20 μg/mL but remained near the upper limit. In Cases 1–4, no methicillin-resistant staphylococci were detected; subsequently, VCM administration was discontinued when the SCr level increased. After discontinuation of only VCM, the originally prescribed antimicrobial drugs, such as meropenem (MEPM) and ceftriaxone, were continued for several days; consequently, patients' meningitis symptoms improved, and the SCr levels also normalized within a week from VCM discontinuation. Moreover, Cases 1–4 received no high-risk AKI drugs such as antirheumatics, immunosuppressives, anticancer drugs, non-steroidal antiinflammatories, and acyclovir.[9,10]

In addition, there were no patients with adverse events such as VIII cranial nerve neuropathy, pancytopenia, and liver dysfunction induced by empirical VCM treatment.

Cerebrospinal Fluid Culture in VCM-Treated Patients Table 3 shows the results of cerebrospinal fluid cultures performed before the administration of the first dose of the antimicrobial drug. Of the study patients, 4 showed positive bacterial culture results, and the other 31 showed negative results. The cultured specimens were distributed as follows: 1 MRSA (Case 5), 2 methicillin-resistant *S. epidermidis* (MRSE) (Cases 6 and 7), and 1 *Klebsiella oxytoca* (Case 8). Based on these results, empirical VCM treatment was switched to definitive treatment in 3 patients who tested positive for MRSA and MRSE. Thus, the incidence rate of bacterial meningitis caused by methicillin-resistant staphylococci was only 8.6% (3/35 cases). In Case 8, in which *K. oxytoca* was detected, VCM administration was terminated within 3 d of initiation.

Factor Analysis of AKI Onset by Empirical VCM Therapy Given the results of Table 3, we divided 32 patients into AKI patients and non-AKI patients, except for Cases 5–7 who received definitive treatment of VCM. We compared the groups' clinical backgrounds (Table 4). There were no significant differences in age, VCM dose, laboratory data, or frequency of concomitant agents. The rate of empirical VCM therapy for a week or more was significantly higher in AKI patients compared with non-AKI patients.

Effectiveness of VCM against MRSA and MRSE Infections Table 5 shows the results of efficacy evaluation in 3 patients with bacterial meningitis who were prescribed VCM treatment.

Case 5 was initially identified as a MRSA infection in a previous hospital. VCM treatment was initiated at our hospi-

Table 2. Details of the Clinical Progress of Patients with Acute Kidney Injuries

	Case 1 (Age 39)	Case 2 (Age 64)	Case 3 (Age 70)	Case 4 (Age 63)
Start value of SCr (mg/dL)	1.9	0.8	0.7	0.6
Maximum value of SCr (mg/dL)	2.9	1.3	1.2	1.1
Body weight (kg)	88.8	65.5	56.5	68.5
Dosage at the start of VCM (/d)	1.5 g × 2	1.5 g × 2	1.25 g × 2	1.5 g × 2
Dosage of VCM per body weight (mg/kg/time)	16.9	22.9	22.1	21.9
Trough concentration of VCM at Day 3 (μg/mL)	19.1	18.1	-	-
at Day 7 (μg/mL)	18.5	19.2	-	-
Treatment period of VCM (d)	10	7	8	7
Concomitant antimicrobial agent	MEPM	CTRX	CTRX	MEPM
Treatment period of MEPM or CTRX (d)	14	20	12	10
Bacterial culture test	Negative	Negative	Negative	Negative

SCr: serum creatinine, VCM: vancomycin, MEPM: meropenem, CTRX: ceftriaxone

Table 3. Cerebrospinal Fluid Culture Results in Patients Treated with Vancomycin

	MRSA (Case 5)		MRSE (Case 6)		MRSE (Case 7)		*Klebsiella oxytoca* (Case 8)		Negative (n = 31)
Antimicrobial agent	MIC	S.I.R.	MIC	S.I.R.	MIC	S.I.R.	MIC	S.I.R.	
CEZ	>16	R	<=4	R	<=4	R	>=64	R	
CTRX	>16	R					<=1	S	
PCG			>0.5	R	>0.5	R			
ABPC/SBT	<=8	R	<=2	R	4	R	8	S	
IPM/CS	4	R	<=1	R	<=1	R	<0.25	S	
MEPM	4	R					<0.25	S	
VCM	1	S	1	S	1	S			
LVFX	>4	R	0.25	S	4	R	<0.12	S	

S.I.R.: S: susceptible, I: intermediate, R: resistant
MRSA: methicillin-resistant *Staphylococcus aureus*, MRSE: methicillin-resistant *Staphylococcus epidermidis*, MIC: minimum inhibitory concentration, CEZ: cefazolin, CTRX: ceftriaxone, PCG: benzylpenicillin potassium, ABPC/SBT: ampicillin/sulbactam, IPM/CS: imipenem/cilastatin, MEPM: meropenem, VCM: vancomycin, LVFX: levofloxacin

Table 4. Comparison of Clinical Background in Patients who Received Empirical VCM Therapy

	Empirical VCM therapy		p-value
	AKI (n = 4)	non-AKI (n = 28)	
Male / Female	3 / 1	13 / 15	0.350
Age (years)	63.5 (45.0 – 68.5)	68.0 (44.5 – 75.0)	0.408
Body weight (kg)	67.0 (56.5 – 83.7)	56.3 (46.0 – 63.5)	0.117
VCM therapy			
Dosage at the start of VCM (g/kg/d)	43.0 (35.9 – 47.7)	43.1 (36.2 – 47.7)	0.864
Treatment period of VCM (d)	7.5 (7.0 – 9.5)	6.0 (3.0 – 10.8)	0.420
VCM treatment period for a week or more (n (%))	4 (100)	9 (32.1)	0.020
Laboratory data			
BT (℃)	39.1 (38.2 – 40.0)	38.0 (37.8 – 38.8)	0.081
WBC ($\times 10^3$ /μL)	17.1 (15.2 – 24.5)	13.6 (9.3 – 17.0)	0.082
CRP (mg/dL)	12.7 (5.1 – 15.0)	5.3 (1.9 – 10.8)	0.220
SCr (mg/dL)	0.8 (0.6 – 1.6)	0.6 (0.5 – 0.8)	0.094
Concomitant agent (n (%))			
Carbapenem	2 (50.0)	13 (46.4)	1.000
3rd and 4th generation cephalosporin	2 (50.0)	12 (42.9)	1.000
Penicillin/β-lactamase inhibitor	0	6 (21.4)	0.566
Quinolone	0	1 (3.6)	1.000
H_2blocker	1 (25.0)	4 (14.3)	1.000
β-blocker	1 (25.0)	2 (7.1)	1.000
Loop diuretic	1 (25.0)	2 (7.1)	1.000

VCM: vancomycin, AKI: acute kidney injury, BT: body temperature, WBC: white blood cell, CRP: C-reactive protein, SCr: serum creatinine
Values are presented as numbers (%) or medians (interquartile ranges).

Table 5. Clinical Course in Patients Treated with Vancomycin

Case 5. MRSA	Age 29	Before administration	Administration period			Evaluation
			Day 3	Day 7	Day 22 (end)	
BT (℃)		39.4	38.2	37.4	36.3	improvement
WBC ($\times 10^3$ /μL)		26.8	7.3	7.6	5.4	improvement
CRP (mg/dL)		14.8	5.3	0.5	0.6	improvement
Bacterial culture test		MRSA	-	negative		disappearance
					Final evaluation	**Improvement**

Case 6. MRSE	Age 26	Before administration	Administration period			Evaluation
			Day 3	Day 7	Day 13 (end)	
BT (℃)		38.1	37.1	36.2	36.2	improvement
WBC ($\times 10^3$ /μL)		14.2	5.9	4.2	5.6	improvement
CRP (mg/dL)		5.8	4.5	4.2	2.1	unchanged
Bacterial culture test		MRSE	-	negative		disappearance
					Final evaluation	**Improvement**

Case 7. MRSE	Age 81	Before administration	Administration period			Evaluation
			Day 3	Day 7	Day 11 (end)	
BT (℃)		39.0	36.7	37.1	36.6	improvement
WBC ($\times 10^3$ /μL)		16.9	5.8	7.6	6.6	improvement
CRP (mg/dL)		38.4	4.9	4.4	3.1	improvement
Bacterial culture test		MRSE	-	negative		disappearance
					Final evaluation	**Improvement**

BT: body temperature, WBC: white blood cell, CRP: C-reactive protein, MRSA: methicillin-resistant *Staphylococcus aureus*, MRSE: methicillin-resistant *Staphylococcus epidermidis*

tal, and VCM was administered for 22 d; subsequently, MEPM was coadministered. The blood trough concentration of VCM on day 3 of administration was 14.7 μg/mL and thereafter fluctuated between 10 and 20 μg/mL. The patient's body temperature reduced and WBC counts and CRP levels improved. Additionally, bacterial elimination was confirmed by a culture test performed after day 7 of VCM administration, verifying the efficacy of VCM.

In Case 6, in which MRSE was detected, VCM was administered for 13 d. The blood trough concentration of VCM on day 3 of administration was low at 8.5 μg/mL; consequently, the dose was adjusted. After day 7, the blood trough concentration of VCM fluctuated between 10 and 15 μg/mL. CRP levels did not improve as per the applied criteria; however, the patient's body temperature reduced and WBC count improved. Bacterial elimination was confirmed by a culture test performed after day 7 of VCM administration; thus, VCM treatment was considered effective.

In Case 7, in which MRSE was detected, VCM was administered for 11 d with the coadministration of ceftriaxone. The blood trough concentration of VCM on day 3 of administration was 12.5 μg/mL and thereafter fluctuated between 10 and 20 μg/mL. The patient's body temperature reduced and WBC counts and CRP levels improved. Bacterial elimination was confirmed by a culture test performed after day 7 of VCM administration, verifying the efficacy of VCM.

DISCUSSION

The incidence rate of bacterial meningitis caused by methicillin-resistant staphylococci is lower than that of bacterial meningitis caused by other gram-positive bacteria.[1,2] However, considering the high mortality rate of staphylococcal infections,[11] the use of empirical VCM therapy becomes more vital, particularly in cases of hospital-acquired bacterial meningitis. Compared with other antimicrobial drugs, VCM is associated with a high frequency of side effects, one of which is renal dysfunction. When administering empirical VCM treatment to patients with suspected bacterial meningitis, understanding and mitigating the associated risks will lead to safer VCM treatment.

In this study, four patients showed AKI onset. Other than VCM, there were many other drugs that could potentially cause AKI.[9,10] However, in this study, we consider that AKI onset was associated with empirical VCM therapy because SCr levels normalized after discontinuation of only VCM. We found that AKI had an incidence rate of 11.4% during empirical VCM treatment. The rate of AKI following VCM therapy has been reported to be approximately 10%, depending on blood concentration.[12,13] Thus, empirical VCM treatment does not significantly increase the occurrence of AKI compared with normal VCM treatment. However, it is crucial to pay sufficient attention to the development of AKI even if VCM is used as empirical therapy. Accordingly, while administering empirical VCM treatment, continuous evaluation of the requirement of this drug, based on both bacterial culture and renal function results, is important.

In this study, the majority of patients treated with empirical VCM therapy had underlying diseases requiring neurosurgery; they had contracted meningitis due to the use of drainage devices. In hospital-acquired cases, it is extremely essential to perform tests for the identification of MRSA and MR-CNS when gram-positive cocci are detected. Therefore, considering that most patients in this study had hospital-acquired infections and were undergoing drainage, option of empirical VCM therapy was an appropriate treatment. In 17 cases, the VCM administration period was less than 1 week, including 2 cases in which VCM was administered for community-acquired

disease but discontinued immediately after bacterial culture results were obtained. In these 17 cases, VCM administration was terminated within 1 week because methicillin-resistant staphylococci were not detected by Gram staining or bacterial culture. None of these 17 patients showed AKI onset. Long-term VCM administration for 1 week or more has been reported as one of the risk factors for AKI onset due to VCM.[13] Our results also indicate that the rate of empirical VCM therapy for a week or more was significantly higher in AKI patients compared with non-AKI patients. The results of general tests performed for bacterial identification are usually obtained within 1 week, depending on the facility environment.[14] Therefore, to avoid AKI associated with empirical VCM treatment, we must first assess the results of Gram staining and bacterial culture to evaluate if VCM administration is required. If VCM is not needed, it is essential to terminate administration within 1 week of initiation. In the 4 cases involving AKI in this study, the cerebrospinal fluid culture was negative at an early stage of the infection, but empirical VCM treatment was continued for more than 1 week. Since this was a retrospective study, we cannot judge whether empirical VCM treatment for 1 week or more was actually needed in the 4 cases involving AKI. However, based on the results of this study, we believe that shortening the VCM administration period, discontinuing the drug, or switching to other antibiotics may have helped avoid the onset of AKI in these patients.

In 2 cases involving AKI onset (Cases 3 and 4), therapeutic drug monitoring (TDM) was not performed. A high trough concentration of VCM (>20 μg/mL) is the strongest risk factor for AKI due to VCM therapy.[13,15] Therefore, the Japanese guidelines recommend performing TDM when VCM is administered for ≥4 d. When an antimicrobial drug is used for suspected bacterial meningitis treatment, a high dose may be used to increase the chances of the drug entering the cerebrospinal fluid. In Cases 3 and 4, higher than usual doses of VCM (2 g/d) were administered, and trough levels may have been high in these patients. Therefore, to reduce the AKI risk, it is important to confirm the blood trough concentration of VCM using TDM.

AKI was noted in Cases 1 and 2 although TDM was performed in these patients. The initial blood trough concentration did not exceed 20 μg/mL in either case but transitioned to a level close to the upper limit. According to the Infectious Diseases Society of America, the target blood trough concentration of VCM is 10–20 μg/mL. The blood trough concentration of VCM must reach 15–20 μg/mL at an early stage due to the recent increase in the minimum inhibitory concentration (MIC).[16] However, van Hal *et al*. reported that an initial blood trough concentration of ≥15 μg/mL increases the risk of AKI.[17] Thus, no conclusion has been reached regarding the safety of a blood trough concentration of VCM of 15–20 μg/mL in the initial stage of treatment. For these reasons, the Japanese TDM guideline advises against setting the trough concentration of VCM at 15–20 μg/mL in the initial stage. In Cases 1 and 2, transition of the blood trough concentrations to values close to the upper limit in the initial stage may have influenced the onset of AKI. These results imply that safer empirical treatment with VCM is required, which can be achieved not only by implementing TDM but also initial dose setting to avoid 15–20 μg/mL in the initial stage. In a previous study, we demonstrated that performing initial dose setting for each patient can reaches the target blood drug level more quickly and safety.[18] Based on the results of the 4 cases involving AKI, the following points can be considered: 1) Even when empirical VCM treatment is implemented, the initial dose setting of VCM should be performed (based on Cases 1 and 2); and 2) TDM should be regularly performed (based on Cases 3 and 4). These two factors will lead to safer empirical treatment using VCM.

In this study, efficacy was confirmed in all 3 cases in which MRSA or MRSE was detected. VCM does not enter the cerebrospinal fluid when the blood-cerebrospinal fluid barrier is in the normal state; however, VCM is known to enter the cerebrospinal fluid from blood if the blood-cerebrospinal fluid barrier is broken down due to meningitis.[19,20] Mihara *et al*. reported that the maximum concentration of VCM in cerebrospinal fluid was 2.1 μg/mL when intravenous-drip infusion of 1 g VCM over 60 min was used in 4 patients with bacterial meningitis after subarachnoid hemorrhage surgery.[21] Moreover, they indicated that there was almost no difference in the half-life of VCM between plasma and cerebrospinal fluid.[21] Therefore, VCM is effective against bacterial meningitis caused by MRSA or MRSE in terms of permeability to cerebrospinal fluid.

Since this was a retrospective, single-center, observational study, some limitations require consideration. Our study had a number of limitations which warrant consideration. (1) Factors, such as concomitant drugs, underlying diseases and meningitis severity could have affected AKI onset. These factors were not sufficiently analyzed due to the small sample size. (2) The diagnosis of AKI was based only on the KDIGO diagnostic criteria using SCr values because the evaluation by urine volume could not be performed. (3) The relationship between blood VCM levels and the onset of AKI was not analyzed because VCM concentrations could not be measured in some patients. (4) Finally, the efficacy of VCM was not evaluated based on cerebrospinal fluid parameters, such as cell counts, glucose levels, and protein levels. To overcome these research limitations, multicenter, prospective, observational studies are necessary in the future.

Conclusions The results of this study indicate that empirical VCM treatment in patients with suspected bacterial meningitis is associated with a risk of AKI. However, because VCM is expected to show antimicrobial effects on methicillin-resistant staphylococci, it would be difficult to exclude empirical VCM treatment from the treatment options for hospital-acquired bacterial meningitis. When administering empirical treatment with VCM, we should consider terminating or modifying the treatment within 1 week of initiation based on results of Gram staining and bacterial culture. Moreover, performing initial dose setting and TDM of VCM will lead to safer empirical treatment of VCM.

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Conflict of interest The authors declare no conflict of interest.

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