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Original Article

Correlation between vancomycin penetration into cerebrospinal fluid and protein concentration in cerebrospinal fluid/serum albumin ratio☆

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ABSTRACT

Bacterial meningitis is a life-threatening condition. Vancomycin (VCM) is one of the antibiotics used as empirical therapy for bacterial meningitis. It is essential to maintain an adequate concentration of VCM in cerebrospinal fluid (CSF) to treat bacterial meningitis effectively. VCM administered intravenously must pass the blood-brain barrier (BBB) to enter the CSF and the extent of VCM penetration into CSF varies widely among patients. Previous report indicated that CSF albumin level is useful for estimation of VCM CSF penetration. However, CSF albumin level is not measured in routine practice. We focused on CSF protein concentration that is generally examined at the beginning of diagnosis and treatment of bacterial meningitis. We examined the relationship between CSF protein concentration/serum albumin ratio and the extent of VCM penetration into CSF.

This retrospective study involved 7 patients admitted to our hospital who were treated with VCM for suspected bacterial meningitis. The VCM concentrations in serum and CSF were 17.6 ± 7.2 μg/mL and 3.31 ± 3.14 μg/mL, respectively. The serum VCM concentrations showed no significant correlation with CSF VCM concentrations. On the other hand, the protein concentration in CSF/serum albumin ratio showed a strong positive correlation with the VCM CSF/serum ratio ($r = 0.877$, $p < 0.005$). Our study indicates that the ratio of CSF protein concentration/serum albumin is likely useful for estimating the approximate VCM CSF/serum ratio. This could contribute to an improvement in the treatment of bacterial meningitis.

1. Introduction

Bacterial meningitis is a life-threatening condition, and patients often suffer severe sequelae even if their lives can be saved. In general, bacterial meningitis is the rapid development of inflammation of the meninges. Therefore, adequate doses of an appropriate antibiotic must be administered immediately from the initial treatment [1].

Gram-positive organisms account for most cases of bacterial meningitis. Due to the emergence of penicillin-resistant Gram-positive organisms (e.g., *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Staphylococcus epidermidis*), vancomycin (VCM) is one of the antibiotics used as empirical therapy for bacterial meningitis. The usual VCM minimum inhibitory concentration (MIC) for staphylococci and streptococci is ≤1 μg/mL [2]. Based on an experimental meningitis model in rabbits, it is hypothesized that the peak concentration of VCM in cerebrospinal fluid (CSF) required for maximal killing activity is more than 4 times the minimum bactericidal concentration [3]. Therefore, it is essential to maintain an adequate concentration of VCM in CSF to treat bacterial meningitis effectively. It has been reported that serum VCM concentration shows a positive correlation with CSF VCM concentration [4]. The recommended target serum trough concentration of VCM

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is 15–20 μg/mL for bacterial meningitis [2]. VCM administered intravenously must pass the blood-brain barrier (BBB) to enter the CSF, but it penetrates poorly into the CSF because of its hydrophilic properties and high molecular weight (1450 Da) [5,6]. In the treatment of bacterial meningitis, its use is based on the hypothesis that the BBB is disrupted when the meninges are inflamed [7]. However, CSF VCM concentrations are lower than expected in some cases with bacterial meningitis, even when serum VCM concentrations are above the recommended level [8]. Thus, it is predicted that different factors other than serum VCM concentration affects the CSF VCM concentration.

The most protein in CSF is derived from serum albumin, but diffusion into CSF is restricted by the BBB under normal condition. Previous reports have shown that CSF albumin levels are elevated in parallel with disruption of BBB, and argued that CSF albumin/serum albumin ratio reflects the extent of BBB disruption [9,10]. In addition, Li et al. indicated that CSF albumin level has a statistically significant positive correlation with CSF VCM concentration and CSF albumin level is useful for estimation of VCM CSF penetration when VCM is administered by continuous intravenous infusion [11]. However, VCM is usually administered by intermittent intravenous infusion and CSF albumin level is not measured in routine practice. On the other hand, the CSF protein concentration is generally examined at the beginning of diagnosis and treatment of bacterial meningitis. If the CSF protein concentration/serum albumin ratio reflects penetration of VCM into CSF, we can estimate the extent of VCM penetration into CSF from the initial treatment. Therefore, we examined the relationship between CSF protein concentration/serum albumin ratio and the extent of VCM penetration into CSF in order to promote the proper use of VCM for the treatment in bacterial meningitis.

2. Patients and methods

2.1. Patients

We extracted laboratory data and outcomes of patients who were treated with intravenous VCM for suspected bacterial meningitis from April 2013 to April 2017. The exclusion criterion was the absence of measurements of VCM concentrations in CSF and serum.

2.2. Drug administration and sample collection

VCM was intravenously administered 2–4 times per day. We adjusted the dosage based on therapeutic drug monitoring (TDM) data to achieve the target serum trough concentrations (15–20 μg/mL) during treatment.

Blood samples were collected just before VCM infusion, when steady state concentrations had been achieved, and after at least 2 days of the dosage regimen.

CSF VCM concentrations were measured retrospectively using residual CSF. Samples were collected through an external ventricular drainage for hydrocephalus or lumbar puncture for CSF examination after steady-state serum concentrations had been achieved.

2.3. Sample analysis

VCM concentrations in serum and CSF were measured by a chemiluminescence immunoassay with an ARCHITECT® analyzer (Abbott Laboratories, Irving, TX, USA). The method was fully validated over a concentration range of 3.0–100.0 μg/mL. The lower limit of quantification (LLOQ) and the lower limit of detection (LLOD) were 3.0 μg/mL and 0.24 μg/mL, respectively. Serum albumin concentrations were measured by bromocresol purple method. CSF protein concentrations were measured by pyrogallol red method. Glucose concentrations in CSF were measured by hexokinase method. CSF cell counts were performed manually.

2.4. Clinical efficacy

Clinical efficacy of VCM was determined based on the previous report [12]. “Effective” means that bacteria in CSF disappeared more than 2 days after treatment. If the culture was negative, “effective” means that main symptom and CSF glucose level improved and cell count in CSF decreased to less than 100 cells/μL during VCM treatment. “Ineffective” means that bacteria in CSF did not disappear during VCM treatment. If the culture was negative, “ineffective” means that above-mentioned improvement was not observed. “Undeterminable” means that we could not judge the clinical efficacy of VCM for some reason.

2.5. Statistical analysis

Data are presented as the mean ± standard deviation. Correlations were calculated using Pearson's correlation test. $P < 0.05$ was considered statistically significant.

Concentrations below the LLOD were treated as one-half of the LLOD in the analysis. Concentrations below the LLOQ and over the LLOD were treated as the arithmetic average of the LLOD and LLOQ in the analysis, according to a previous report [8].

2.6. Ethical approval

Ethical approval was obtained from the medical research ethics committee at Chiba University (No. 2743). The information disclosure document associated with this study is available on the hospital's website. Patients were notified about their participation in the study and informed that they were free to opt out of study participation at any time.

3. Results

Seven patients fulfilled our criteria. The patient characteristics and CSF findings at the beginning of treatment are shown in Table 1. The mean cell count and the glucose and protein concentrations in CSF were 581 ± 803 cells/μL, 48.3 ± 23.6 mg/dL, and 312.9 ± 459.4 mg/dL, respectively.

Table 2 shows the serum and CSF VCM concentrations and clinical efficacy of VCM. In the patient No. 2 and No. 4, an external ventricular drainage for hydrocephalus was performed during VCM treatment and CSF VCM concentrations were measured using samples collected through the drainage. VCM concentrations in CSF were measured twice at different times during the administration of VCM in only 1 patient (No. 4). Therefore, we used 8 VCM concentrations in CSF in the analysis. VCM concentrations in serum and CSF were 17.6 ± 7.2 μg/mL and 3.31 ± 3.14 μg/mL, respectively. In 3 cases, the VCM concentrations in CSF were below the LLOQ. The CSF/serum ratio was 0.180 ± 0.152 (range 0.010–0.431). Serum VCM concentrations showed no significant correlation with CSF VCM concentrations ($r = 0.462$, $p = 0.201$, Fig. 1). In addition, the VCM CSF/serum ratio showed no significant correlation with cell count ($r = 0.483$, $p = 0.225$) or glucose levels ($r = -0.542$, $p = 0.165$) in CSF. On the other hand, protein concentrations in CSF/serum albumin ratio showed a strong positive correlation with the VCM CSF/serum ratio ($r = 0.877$, $p < 0.005$, Fig. 2).

The VCM concentration in CSF from patient No. 2 was below the LLOD. Furthermore, the VCM MIC for *staphylococcus epidermidis* in CSF increased from 1 μg/mL to 2 μg/mL and C-reactive protein rose from 0.1 mg/dL to 6.3 mg/dL during the treatment. It was

Table 1
Patient characteristics and CSF findings at the beginning of treatment.

Patient characteristics					Cerebrospinal fluid parameters			
Patient number	Sex	Age (year)	Body weight (kg)	eGFR (mL/min/1.73 m^2)	Culture	Cell count (cells/μL)	Glucose (mg/dL)	Protein (mg/dL)
1	Male	38	63.8	92.2	Negative	281	68	86
2	Female	61	64.5	86.1	*Staphylococcus epidermidis* (MIC = 1)	520	79	50
3	Female	70	49.1	74.1	*Enterococcus faecium* (MIC = 1)	586	38	138
4	Female	17	27.8	96.0	*Corynebacterium striatum* (MIC = 0.5)	290	50	44
5	Male	36	79.2	69.4	Negative	2337	20	1263
6	Male	53	72.2	93.2	*Staphylococcus capitis* (MIC = 1)	1	64	44
7	Female	17	56.3	173.2	Negative	54	19	569

Table 2
Serum and CSF VCM concentrations and clinical efficacy of VCM.

Patient number	Serum VCM concentration (μg/mL)	CSF VCM concentration (μg/mL)	VCM CSF/serum ratio	CSF protein (mg/dL)	Serum albumin (g/dL)	Clinical efficacy of VCM
1	25.7 (day 4)	4.60 (day 3)	0.179	169 (day 3)	3.7 (day 3)	Effective
2	12.0 (day 4)	<0.24 (day 4)	0.010	23 (day 4)	3.9 (day 4)	Ineffective
3	11.2 (day 4)	3.50 (day 4)	0.313	124 (day 4)	3.1 (day 4)	Ineffective
4	27.7 (day 7)	<3.0 (day 6–8)	0.058 (day 7)	44 (day 1)	2.5 (day 7)	Effective
	9.8 (day 10)	<3.0 (day 10–11)	0.149 (day 10)	25 (day 14)	3.1 (day 10)	
5	21.6 (day 14)	9.32 (day 14)	0.431	325 (day 14)	3.9 (day 14)	Effective
6	11.8 (day 3)	<0.24 (day 2)	0.010	44 (day 2)	2.8 (day 2)	Undeterminable
7	20.7 (day 5)	5.60 (day 5)	0.271	229 (day 5)	3.8 (day 5)	Undeterminable
mean ± standard deviation	17.6 ± 7.2	3.31 ± 3.14	0.180 ± 0.152	123 ± 111	3.4 ± 0.5	

considered that the meningitis could worsen with low concentrations of VCM in CSF. Therefore, VCM was switched to linezolid (LZD) and the bacterial meningitis subsequently improved. In the patient No. 3, although the CSF VCM concentration (3.50 μg/mL) was over the VCM MIC for *Enterococcus faecium*, VCM was ineffective. In the patient No. 4, although CSF VCM concentration was below the LLOQ (3.0 μg/mL), VCM was effective. In the patient No. 6, cerebrospinal fluid examination was not performed at the proper timing during VCM treatment because treatment target was not certain. In the patient No. 7, VCM administration was stopped on day 8 because tuberculous meningitis was suspected. Therefore, we could not judge the clinical efficacy of VCM in the patient No. 6 and 7.

4. Discussion

In this study, protein concentration in CSF/serum albumin ratio showed a strong statistically significant positive correlation with the VCM CSF/serum ratio. Our study indicates that CSF protein concentration/serum albumin ratio is likely useful for estimating the approximate VCM CSF/serum ratio. This could contribute to an improvement in the treatment of bacterial meningitis.

Ichie et al. reported that the patients in the cerebral fluid drainage group showed a significantly lower serum VCM concentration than in the non-drainage group [14]. They considered that cerebral fluid drainage might contribute the drug removal from the CSF and affect serum VCM concentrations. Our study includes 2 cases receiving cerebrospinal fluid drainage (the patient No. 2 and No. 4). The CSF VCM concentrations in these cases were below the LLOD (0.24 μg/mL) or LLOQ (3.0 μg/mL), and the amount of cerebral fluid drainage was 200–300 mL per day. Therefore, we considered that cerebral fluid drainage did not largely affect the serum VCM concentrations in our study.

Generally, drugs administered intravenously tend to show slightly higher concentrations in lumbar CSF than ventricular CSF [5]. In the patient No. 2 and No. 4, the CSF collected through an external ventricular drainage was used for measuring CSF VCM concentrations. Although the difference in sample collection might affect the CSF VCM concentrations, the effect has not been well

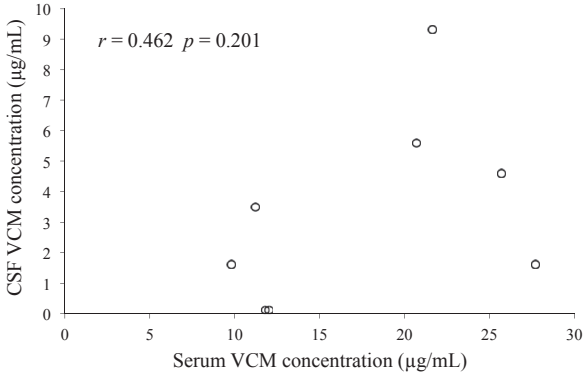

Fig. 1. The relationship between serum VCM and CSF VCM concentrations. The correlation coefficient is represented by *r*.

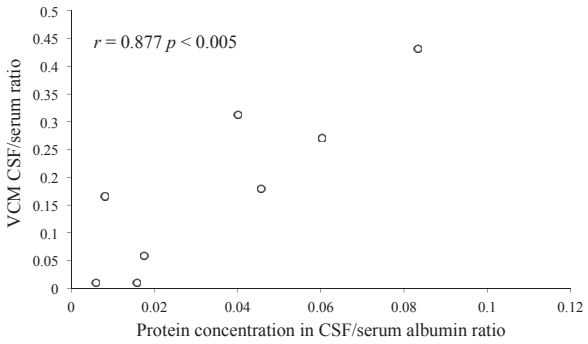

Fig. 2. The relationship between protein concentration in CSF/serum albumin ratio and VCM CSF/serum ratio. VCM CSF/serum ratio, CSF protein and serum albumin level in Table 2 were used in the analysis. The correlation coefficient is represented by *r*.

documented [7]. Further study will be needed to clarify the influence of difference in sample collection on CSF VCM concentration.

Penetration of VCM into CSF may decrease with improvement of meningeal inflammation [15]. In this study, CSF VCM concentration was measured after 7 days or more have passed since the treatment started in 2 cases. In the patient No. 4, although the CSF VCM concentration was measured on day 6–8 and day 10–11, the CSF protein concentration did not largely change during the treatment. Therefore, the late measurement of CSF VCM concentration might not largely affect the VCM CSF concentration in this case. In the patient No. 5, the VCM CSF concentration was measured on day 14. The protein concentration in CSF on day 14 (325 mg/dL) was lower than that at the beginning of treatment (1263 mg/dL). Therefore, improvement of inflammation and decrease in CSF protein concentration could affect the CSF VCM concentration.

In conflict with our study, the previous report have shown that serum VCM concentration show a statistically significant positive correlation with CSF VCM concentration [4]. In Ricard et al.'s report, CSF protein concentrations were relatively higher than the present study [4]. This indicates that disruption of BBB was more severe, resulting in higher VCM CSF/serum ratio. This is probably why serum VCM concentration showed a statistically significant positive correlation with CSF VCM concentration in their report. In our study, CSF protein concentrations were relatively lower than their report, resulting in lower VCM CSF/serum ratio. This could be the reason why serum VCM concentration showed no significant correlation with CSF VCM concentration in our study. According to the systematic review, the relationship between serum VCM concentration and CSF VCM concentration seems to remain unclear [7]. Absence of CSF protein concentration/serum albumin ratio data in the previous reports may make the relationship complicated. The relationship between serum VCM concentration and CSF VCM concentration may become clearer with the accumulation of data on CSF protein concentration/serum albumin ratio.

Previous reports argued that CSF albumin/serum albumin ratio reflects the extent of BBB disruption [9,10]. As shown in our study, VCM seems to penetrate into CSF well when the CSF protein concentration is elevated. Li et al. similarly indicated that CSF albumin levels have a statistically significant positive correlation with CSF VCM concentrations when VCM is administered by continuous intravenous infusion [11]. In this retrospective study, we used total CSF protein concentrations instead of CSF albumin levels for the analysis because CSF albumin levels had not been measured. Our results support the measure of total CSF protein concentrations to estimate the CSF VCM concentration when VCM is administered by intermittent intravenous infusion. This may allow us to estimate the approximate CSF VCM concentration at the beginning of treatment for bacterial meningitis because the cerebrospinal fluid is generally examined at that stage. Based on the results, we can choose an appropriate antimicrobial agent and optimize the dosage of VCM for bacterial meningitis from the onset. These steps could contribute to the successful treatment of bacterial meningitis.

CSF protein levels are known to be relatively low (<200 mg/dL) in patients with bacterial meningitis caused by coagulase-negative staphylococci (CNS) [16–19]. Patients No. 2 and No. 4, who had CNS, had CSF VCM concentrations below the LLOD (0.24 μg/mL). Mounier et al. reported that CSF VCM concentrations are low (<1.1–2.6 μg/mL) in patients with bacterial meningitis caused by CNS and they are associated with low CSF protein levels (<150 mg/dL) [8]. Thus, in cases with low CSF protein levels, we should consider whether to continue with VCM treatment or switch to another antimicrobial agent depending on the clinical situation. For example, LZD may be more appropriate in patients with low CSF protein levels because it enters the CSF in high enough amounts (50–70% of serum) regardless of BBB disruption [20].

In the patient No. 1, 2 and No. 5, clinical efficacy of VCM were associated with high or low VCM CSF concentrations. On the other hand, the reason for lack of association in the patient No. 3 and No. 4 might be as follows. In the patient No. 3, persistent bacteria infection was suspected because CSF leaks was observed during VCM treatment. In the patient No. 4, the actual VCM CSF concentration might be higher than the VCM MIC for *Corynebacterium striatum* (0.5 μg/mL). In this retrospective study, several factor other than CSF VCM concentration probably affected the clinical status.

There were some limitations to our study. First, we evaluated a small number of cases. Therefore, the heterogeneity of the cases might have affected the results. Further study with a large number of cases will be needed to confirm our results. Second, there was a time lag between the collection of serum and CSF. However, it may not have had a substantial effect on the results because CSF VCM concentrations are relatively stable regardless of the time after administration [21,22]. Third, some CSF VCM concentrations were below the LLOQ or LLOD, and we used replacement values for analysis, according to a previous report [13]. We may have to improve the quantitative sensitivity to achieve a more accurate analysis.

In conclusion, protein concentration in CSF/serum albumin ratio showed a strong positive and statistically significant correlation with VCM CSF/serum ratio in patients with bacterial meningitis. Our results indicate that protein concentration in CSF/serum albumin ratio is likely useful for estimating the approximate extent of VCM entry into CSF at the start of treatment. This could contribute to the proper use of VCM for the treatment of bacterial meningitis.

Conflicts of interest

None.

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References

[1] Nau R, Djukic M, Spreer A, Ribes S, Eiffert H. Bacterial meningitis: an update of new treatment options. Expert Rev Anti Infect Ther 2015;13:1401–23.
[2] Rybak M, Lomaestro B, Rotschafer J, Moellering RJ, Craig W, Billeter M, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American society of health-system pharmacists, the infecious diseases society of America, and the society of infectious diseases pharmacists. Am J Health Syst Pharm 2009;66:82–98.
[3] Ahmed A, Jafri H, Lutsar I, McCoig CC, Trujilo M, Wubbel L, et al. Pharmacodynamics of vancomycin for the treatment of experimental penicillin- and cephalosporin-resistant pneumococcal meningitis. Antimicrob Agents Chemother 1999;43:876–81.
[4] Ricard JD, Wolff M, Lacherade JC, Mourviller B, Hidri N, Barnaud G, et al. Levels of vancomycin in cerebrospinal fluid of adult patients receiving adjunctive corticosteroids to treat pneumococcal meningitis: a prospective multicenter observational study. Clin Infect Dis 2007;44:250–5.
[5] Nau R, Sorgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. Clin Microbiol Rev 2010;23:858–83.
[6] Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. Clin Infect Dis 2006;1(42 Suppl 1):S35–9.
[7] Beach JE, Perrott J, Turgeon RD, Ensom MHH. Penetration of vancomycin into the cerebrospinal fluid: a systematic review. Clin Pharmacokinet 2017;56:1479–90.
[8] Mounier R, Lobo D, Hulin A, Nebbad B, Cook F, Dhonneur G. Is first-line vancomycin still the best option to treat staphylococcus health care-associated meningitis? World Neurosurg 2017;99:812.e1–5.
[9] Tumani Hayrettin, Hegen Harald. CSF albumin: albumin CSF/serum ratio (marker for blood-CSF barrier function). Cerebrospinal Fluid Clin Neurol 2015:111–4.
[10] Akaishi T, Narikawa K, Suzuki Y, Mitsuzawa S, Tsukita K, Kuroda H, et al. Importance of the quotient of albumin, quotient of immunoglobulin G and

Reibergram in inflammatory neurological disorders with disease-specific patterns of blood-brain barrier permeability. Neurol Clin Neurosci 2015;3:94–100.
[11] Li X, Wu Y, Sun S, Mei S, Wang J, Wang Q, et al. Population pharmacokinetics of vancomycin in postoperative neurosurgical patients. J Phram Sci 2015;104:3960–7.
[12] Fujii R, Kobayashi Y, Nishimura T, Sunakawa K, Iwata S, Meguro H, et al. Criteria for clinical evaluation of antibiotics in the pediatric field. Jpn J Antibiot 2003;51:144–51 (in Japanese).
[13] Abe T, Iwasaki M. Estimation of regression parameters from data with detection and quantitation limits. J Facul Sci Technol Seikei Univ 2006;43:17–21 (in Japanese).
[14] Ichie T, Urano K, Suzuki D, Okada T, Kobayashi N, Hayashi H, et al. Influence of cerebrospinal fluid drainage on the pharmacokinetics of vancomycin in neurosurgical patients. Pharmazie 2015;70:404–9.
[15] Shoukouhi S, Alavi Darazam I. Determination of vancomycin trough level in serum and cerebrospinal fluid of patients with acute community-acquired meningitis: a prospective study. J Infect 2014;69:424–9.
[16] Huang CR, Lu CH, Wu JJ, Chang HW, Chien CC, Lei CB, et al. Coagulase-negative staphylococcal meningitis in adults: clinical characteristics and therapeutic outcomes. Infection 2005;33:56–60.
[17] Mounier R, Lobo D, Cook F, Fratani A, Attias A, Martin M, et al. Clinical, biological, and microbiological pattern associated with ventriculostomy-related infection: a retrospective longitudinal study. Acta Neurochir (Wien) 2015;157:2209–17.
[18] Scheithauer S, Bürgel U, Ryang YM, Haase G, Schiefer J, Koch S, et al. Prospective surveillance of drain associated meningitis/ventriculitis in a neurosurgery and neurological intensive care unit. J Neurol Neurosurg Psychiatry 2009;80:1381–5.
[19] Rammos S, Klopfenstein J, Augspurger L, Wang H, Wagenbach A, Poston J, et al. Conversion of external ventricular drains to ventriculoperitoneal shunts after aneurysmal subarachnoid hemorrhage: effects of site and protein/red blood cell counts on shunt infection and malfunction. J Neurosurg 2008;109:1001–4.
[20] Myrianthefs P, Markantonis SL, Vlachos K, Anagnostaki M, Boutzouka E, Panidis D, et al. Serum and cerebrospinal fluid concentrations of linezolid in neurosurgical patients. Antimicrob Agents Chemother 2006;50:3971–6.
[21] Wang Q, Shi Z, Wang J, Shi G, Wang S, Zhou J. Postoperatively administered vancomycin reaches therapeutic concentration in the cerebral spinal fluid of neurosurgical patients. Surg Neurol 2008;69:126–9.
[22] Autmizguine J, Moran C, Gonzalez D, Capparelli EV, Smith PB, Grant GA, et al. Vancomycin cerebrospinal fluid pharmacokinetics in children with cerebral ventricular shunt infections. Pediatr Infect Dis J 2014;33:e270–2.