Association Between Vancomycin Blood Brain Barrier Penetration and Clinical Response in Postsurgical Meningitis

Qing Wang¹, Si Chen², Yan-Gang Zhou¹, Ping Xu¹, Yi-Ping Liu¹, Hua-Lin Cai¹, Hong Chen¹, Zheng Luo³, Hoan Linh Banh⁴

¹The Second Xiangya Hospital of Central South University, Department of Pharmacy/Institute of Clinical Pharmacy, Changsha, Hunan, P.R. China; ²The Second hospital of Xiangxiang, Department of Pharmacy, Xiangtan, Hunan, P.R. China; ³The Second Xiangya Hospital of Central South University, Department of Neurosurgery, Changsha, Hunan, P.R. China; ⁴University of Alberta, Faculty of Medicine and Dentistry, Department of Family Medicine, Edmonton, AB, Canada.

Received, March 6, 2017; Revised, May 28, 2017; Accepted May 29, 2017; Published May 29, 2017.

ABSTRACT - PURPOSE: This study investigated the association between vancomycin blood brain barrier penetration and clinical response in patients with postsurgical meningitis.

METHODS: Adult patients with postsurgical meningitis were recruited. Eligible patients received vancomycin 500 mg every 6 h for at least 5 days. On day 3 or 4, cerebrospinal fluid (CSF) and simultaneous serum samples were obtained to determine CSF minimum concentrations (Cmin), serum Cmin and CSF to serum Cmin ratio.

RESULTS: Twenty-two patients (14 men and 8 women; mean age of 52.6± 12.1 years) were recruited. The vancomycin Cmin was 3.63 ± 1.64 mg/L in CSF and 13.38 ± 5.36 mg/L in serum, with the CSF to serum Cmin ratio of 0.291 ± 0.118. The Cmin in serum and in CSF showed a significant correlation (p=0.005, r=0.575). The vancomycin CSF Cmin had a significant correlation with the decline of white blood cell counts (WBCs) in CSF (p=0.003, r=0.609). CSF Cmin, serum Cmin and CSF to serum Cmin ratio all showed no significant correlation with clinical response (p=0.335, 0.100, 0.679, respectively).

CONCLUSIONS: There was a positive correlation between serum Cmin and CSF Cmin. However, only CSF Cmin is positively correlated with WBCs improvement in CSF. All other parameters such as serum Cmin, CSF Cmin and CSF to serum Cmin ratio had no correlation with clinical response.

This article is open to POST-PUBLICATION REVIEW. Registered readers (see “For Readers”) may comment by clicking on ABSTRACT on the issue’s contents page.

INTRODUCTION

Central nervous system (CNS) infection such as meningitis, is one of the serious complications in neurosurgical procedures. A recent meta-analysis in post-neurosurgical patients showed that the overall CNS infection was 4.24%, and Gram-positive bacteria was the most common pathogen, accounting for approximately 61.7% of the isolates (1). As resistance to cephalosporins and other β-lactams is increasing, vancomycin has become the antibiotic of choice to eradicate methicillin-resistant Staphylococcus aureus (MRSA). Vancomycin has poor penetration into the cerebral spinal fluid (CSF) (2). The penetrability of vancomycin depends on the degree of meningeal inflammatory when given intravenously (3). Insufficient vancomycin dosage is one of the major proposed causes of treatment failure in MRSA infections (3). Published pharmacokinetics studies on vancomycin in patients with meningitis are mainly focused on vancomycin concentrations in the CSF and/or serum, but not on the CSF exposure-effect relationship (4-7). Using concentrations of vancomycin in serum to predict the clinical response in patients with meningitis remains controversial. The primary objectives of this study were i) to determine the correlation between vancomycin concentrations in CSF and in serum, and ii) to determine the association between vancomycin blood brain barrier (BBB) penetration and clinical response in patients with postsurgical meningitis.

METHODS

Patient population

This prospective study was conducted in the Second Xiangya Hospital of Central South University between May 2014 and June 2015.

Corresponding Author. Ping Xu, The Second Xiangya Hospital of Central South University, Department of Pharmacy/Institute of Clinical Pharmacy, Changsha, Hunan, P.R. China 410011; E-mail address: xuping1109@csu.edu.cn.
The study was carried out according to the declaration of Helsinki and was approved by the Second Xiangya Hospital of Central South University Ethics Committee. All patients consented to participate in the study. All patients aged 18 or older, who were hospitalized in Neurosurgery ward with proven or highly suspected postsurgical meningitis were recruited to the study. Postsurgical meningitis was defined as two or more of the following criteria: 1) clinical signs and symptoms such as fever (temperature greater than or equal to 38°C), headache, vomiting, any meningeal signs, such as, neck rigidity or loss of consciousness; 2) at least two of the changes in CSF specimens: white blood cells (WBCs) count more than 1000×10⁶/L, with coenocyte predominance (>50%), glucose concentrations <2.5 mmol/L, protein concentrations >500 mg/L; 3) either positive result in gram stain culture from the CSF or positive CSF culture (8, 9). All patients received either vancomycin alone or combination therapy with ceftriaxone. All patients had normal hepatic function (serum alanine aminotransferase, (ALT) 9.0-50.0 μL; serum aspartate aminotransferase, (AST), 15.0-40.0 μL; total bilirubin, (TBIL), 5.1-17.1 μmol/L; direct bilirubin, (DBIL), 0-6.0 μmol/L; albumin, (ALB), 40.0-55.0 g/L); and renal function (blood urea nitrogen, BUN, 2.90-7.14 mmol/L; serum creatinine, S_cr, 40.0-133.0 μmol/L; fluid input and urinary output before vancomycin administration.

Drug administration and sample determination
Vancomycin was administrated 500 mg intravenously (iv) every 6 hours (infused over 1 hour) for alone or in combination with Ceftriaxone (2 g iv twice daily). All patients did not administrate corticosteroids during the Vancomycin therapy. CSF and serum samples were collected for vancomycin concentrations by lumbar puncture or lumbar drainage on the day 3 or 4. CSF and serum samples were obtained simultaneously from study patients 5 hours after the end of infusion, to determine the vancomycin minimum concentration (C_min). Vancomycin concentrations were analyzed and CSF to serum C_min ratio was calculated as BBB penetration rate.

Clinical response
The clinical response was evaluated by patients attending physicians and pharmacists together on the basis of patients clinical signs and symptoms of meningitis (including fever, headache, neck rigidity, Brzezinski’s and Kerning’s signs), and laboratory indexes (including biochemical and microbiological examination of CSF), which were observed at baseline (admission) and during hospital stay. Patients defined clinical response was agreed by the treatment team. Cure was defined as all resolution of clinical signs and symptoms of infections, all CSF indexes normalization (including glucose concentrations, protein concentrations and WBCs count), negative culture and gram stain of CSF, and no extra use of other antimicrobial agent. Improvement was defined as partial resolution of clinical signs and symptoms of infection; or CSF indexes obviously improving but not completely returning to normal. Failure was defined as more than 5 days with persistent clinical signs and symptoms of infections and obviously worsening CSF indexes; or persistent positive cultures or gram stain of CSF after 5 days of vancomycin therapy; or a change to another antimicrobial agents (linezolid in particular) against Gram-positive bacteria after 5 days of vancomycin therapy.

The adverse reactions
Daily monitoring of flushing, erythema, urticarial and pruritus for Red Man syndrome due to rapid infusion rate. Nephrotoxicity is a potential side effect from vancomycin. Vancomycin-induced nephrotoxicity was defined as a repeated (at least two consecutive) increased creatinine concentrations in serum of 44.2 μmol/L, or ≥50% increase from baseline without an obvious explanation (10, 11).
Also, blood and the lymphatic system disorders (including thrombocytopenia, neutropenia, agranulocytosis and eosinophilia) were monitored (12).

**STATISTICAL ANALYSIS**

Statistical Package for the Social Sciences (SPSS) version 17.0 was used for descriptive statistical analysis. Mean values and standard deviation were determined for all continuous variables. Vancomycin serum C\textsubscript{min} were stratified into two groups (<15 and \geq 15 mg/L, a consensus review recommended vancomycin serum C\textsubscript{min} at least 15 mg/L to achieve AUC /MIC\geq400) (13). Independent sample 2 tail \(t\)-test and Fisher’s exact test were used for comparison of data in the two groups. The rank correlation was used to analyze the association between vancomycin concentrations (including serum C\textsubscript{min} and CSF C\textsubscript{min}) and clinical response, and between BBB penetration rate and clinical response. Pearson’s \(r\) coefficient was used to evaluate the correlation between vancomycin C\textsubscript{min} and decline of WBCs in the CSF. \(p\leq0.05\) were considered statistically significant.

**RESULTS**

Twenty-two patients (14 men and 8 women) (Table 1) with proven or highly suspected postsurgical meningitis were included in the study. The mean age (\pm SD) was 52.6\pm12.1 years (range, 25-74 years). The baseline mean (\pm SD) glucose concentrations, protein concentrations and WBCs count in the CSF were 2.34 \pm 1.26 mmol/L, 2671.59 \pm 60.11 mg/L, 1819.1\times10^6 /L, respectively. All patients had normal creatinine clearance. Six patients (patients 2, 3, 4, 7, 9 and 13) had positive CSF cultures, and the isolated organisms were Streptococcus pneumoniae (S.pneumoniae), Enterococcus faecium (E.faecium), Staphylococcus aureus (S.aureus), Coagulase-negative staphylococcus, Staphylococcus saprophyticus (S.saprophyticus) and Enterococcus hirae (E.hirae), respectively. After 3 days of therapy, all CSF cultures were negative.

The mean vancomycin C\textsubscript{min} was 3.63 \pm 1.64 mg/L in CSF and 13.38 \pm 5.36 mg/L in serum, and the corresponding CSF to serum C\textsubscript{min} ratio was 0.291 \pm 0.118 (Table 1). The serum and CSF C\textsubscript{min} displayed a weak positive correlation (\(p=0.005, r=0.575\)) (Figure 1). After 3-5 days of therapy, all patients showed amelioration of initial signs and symptoms, and were afebrile. Among them, 54.5% (12/22) were cured, and 45.5% (10/22) improved after 3-5 days.

Vancomycin was continued beyond 5 days in two of the patients with improved signs and symptoms and lumbar drainage was obtained during the extended therapy. Meropenem 2 g iv every 8 hours was initiated in one of the two patients after 3 days of vancomycin therapy. The remaining 8 improved patients were treated with intravenous combined with intraventricular vancomycin 10 mg every other day for 10 days before cure was obtained. No vancomycin-induced nephrotoxicity was observed in all patients and serum creatinine concentrations remained stable during the study.

![Figure 1. Correlation between vancomycin minimum concentrations in CSF and serum, 22 samples\((r=0.575, p=0.005)\). The boldface dot shows two similar data.](image)

Patients achieved cure and those with clinical improvement had no statistical significant difference in CSF C\textsubscript{min}, serum C\textsubscript{min} and CSF to serum C\textsubscript{min} ratio (\(p=0.578, t=0.565; p=0.084, t=1.818; p=0.394, t=-0.871\)). There was no significant difference in clinical response between patients with serum C\textsubscript{min} over 15 mg/L and under 15 mg/L (\(p=0.666\)). A positive correlation between the CSF C\textsubscript{min} and the decline of WBCs in the CSF was obtained after vancomycin treatment (\(p=0.003, r=0.609\)) (Figure 2), while no significant correlation between the serum C\textsubscript{min} or CSF to serum C\textsubscript{min} ratio and the decline of WBCs in the CSF (\(p=0.295, r=0.240; p=0.294, r=0.240\), respectively). CSF C\textsubscript{min}, serum C\textsubscript{min} and CSF to serum C\textsubscript{min} ratio had no significant correlation with clinical response (\(p=0.335, r_s=-0.216; p=0.100, r_s=-0.360; p=0.679, r_s=0.094\), respectively).
DISCUSSION

The pharmacologic action of vancomycin is greatly dependent on CNS penetration which is affected by tissue distribution, and meningeal inflammation (4). To the best of our knowledge, this is the first study focused on the association between vancomycin penetration into CNS and clinical response in patients with postsurgical meningitis. Manufacturer recommended dose of vancomycin is 500 mg iv every 6 hours or 1000 mg iv every 12 hours. In this study, 500 mg iv every 6 hours was used due to physicians’ preference. Clinicians adjust dosage based on patients’ creatinine clearance (Clcr) or serum vancomycin concentrations. In this hospital, it is conventional that the first vancomycin concentrations in serum were monitored on day 3 or later, and in neurosurgery, lumbar punctures are done every other day or every other two days. Therefore, all samples was collected on day 3 or 4, in view of the clinical feasibility of sampling and samples were timely processed. In this study, the average time to process a lumbar puncture was on day 3. In addition, the combination of vancomycin plus ceftriaxone was used for patients with negative culture of CSF, to cover the major Gram-positive and Gram-negative strains.

In this study, one isolate of *S. Pneumoniae* (patient 2) was resistant to chloramphenicol and sulfamethoxazole/trimethoprim. This patient received ceftriaxone prior to enrolment to the study but did not show clinical improvement. This suggests that *S. Pneumoniae* was β-lactam resistant. Therefore, additional therapy of vancomycin was added to increase coverage. CNS infection due to *E. faecium* is rare. While in this study, patient 3, with persistent fever, headache, and lethargy, had a positive CSF culture for *E. faecium* which was only sensitive to vancomycin, teicoplanin and linezolid. This patient received vancomycin alone and clinical symptoms were improved after 7 days of vancomycin therapy and cure was achieved after 14 days of therapy. On day 3, this patient achieved a serum *C*<sub>min</sub> of 15.73 mg/L, which reached the recommended target serum levels for meningitis (15-20 mg/L), but a relative low CSF *C*<sub>min</sub> of 2.57 mg/L (13). According to the latest antimicrobial susceptibility surveillance of Gram-positive bacterial in China, the minimal inhibitory concentration (MIC) for vancomycin-sensitive *E. faecium* was 2 mg/L (5). Published pharmacokinetic-pharmacodynamic studies showed that vancomycin trough concentrations at 4-5 times the MIC best predicted clinical outcomes, and that vancomycin concentrations at 5-10 mg/L had maximum bactericidal activity in human CSF in vitro (3,14). Therefore, the CSF concentrations of 2.57 mg/L obtained in patient 3 might not be the optimal concentration, and higher CSF concentrations (8-10 mg/L) may have been needed to obtain a goal of four or five times above MIC to prevent the occurrence of vancomycin-intermediate or vancomycin-resistant *E. faecium*. The isolated *S. aureus*, *Coagulase-negative staphylococcus* and *S. saprophyticus* in this study were all resistant to cephalosporins and other β-lactam agents. Patient 13 had a CSF positive culture with *E. hirae*, which was Ciprofloxacin-intermediate sensitive and sensitive to vancomycin. Vancomycin was administered for 3 days, and patient had partial improvement of CSF indexes but headaches persisted. Subsequently lumbar drainage and combination therapy of meropenem 2 g iv every 8 hours was initiated.

Vancomycin has reported poor penetration into the uninflamed meningitis, with CSF concentrations of 0-3.45 mg/L and CSF to serum concentration ratio of 0-0.18 (4). Among patients with inflamed meningitis, vancomycin penetration into the CNS increased with CSF concentrations of 6.4-11.1 mg/L and CSF to serum concentration ratios of 0.36-0.48 (13). In this study, patients were given vancomycin as regular regimen of 500 mg iv every 6 hours, and the results showed that CSF *C*<sub>min</sub> varied widely (ranging from 1.44 to 8.51 mg/L, with mean (±SD) of 3.63 ± 1.64 mg/L) and simultaneous CSF to serum
Cmin ratio ranged from 0.163 to 0.570 (mean (±SD), 0.291 ± 0.118). Also, 12 patients achieved CSF Cmin under 3.45 mg/L and 20 patients under 6.40 mg/L. In the 6 patients with positive CSF culture, the CSF Cmin ranged from 2.57 to 4.57 mg/L and 50% (3/6) of these patients achieved CSF Cmin under 3.45 mg/L. The results suggested that CNS penetration of vancomycin was limited and that partial patients with postsurgical meningitis might achieve subtherapeutic CSF concentrations when the drug was given intravenously as regular regimen (500 mg, q6h). The results also indicated that this dose is perhaps inadequate for some patients. The variability of vancomycin penetrating the BBB is shown in some studies. CSF Cmin of 1.6-11.1 mg/L, with a mean CSF to serum C min ratio of 0.29 was reported in patients with bacterial meningitis (15). Patients with pneumococcal meningitis obtained CSF Cmin of undetectable to 22.3 mg/L (6, 16). Another study showed that sufficient vancomycin Cmin of 7.5 to 13.0 mg/L (mean, 11.2 mg/L) in CSF were obtained in 27 patients with acute community acquired meningitis after 3 days of treatment of vancomycin at a dose of 15 mg/kg every 12h (17).

### Table 1. Vancomycin Cmin in CSF and serum, CSF-to-serum Cmin ratio, and clinical response

| Patient | Age(y) | Sex | Weight (kg) | Baseline Scr (μmol/L) | Baseline CLcr (ml/min) | CSF Cmin(mg/L) | Serum Cmin(mg/L) | CSF/serum ratio | Clinical response |
|---------|--------|-----|-------------|-----------------------|-----------------------|----------------|----------------|----------------|-----------------|
| 1       | 74     | M   | 65          | 70.2                  | 74.5                  | 2.97           | 16.9           | 0.176          | Cured           |
| 2*      | 50     | M   | 62          | 92.1                  | 74.1                  | 2.89           | 15.31          | 0.19           | Cured           |
| 3*      | 58     | M   | 71          | 151.4                 | 47.0                  | 2.57           | 15.73          | 0.163          | Cured           |
| 4*      | 60     | F   | 55          | 57.9                  | 79.0                  | 3.63           | 17.37          | 0.209          | Cured           |
| 5       | 57     | M   | 59          | 73.3                  | 81.7                  | 4.73           | 10.95          | 0.432          | Cured           |
| 6       | 50     | M   | 55          | 59                    | 67.8                  | 4.62           | 20.58          | 0.224          | Improved        |
| 7*      | 55     | M   | 60          | 67.3                  | 92.6                  | 4.57           | 13.71          | 0.333          | Improved        |
| 8       | 62     | F   | No          | 51.4                  | No                    | 4.29           | 11.29          | 0.38           | Cured           |
| 9*      | 58     | M   | No          | 76.3                  | No                    | 2.86           | 7.41           | 0.386          | Cured           |
| 10      | 56     | M   | 70          | 115.3                 | 62.3                  | 7.17           | 28.6           | 0.251          | Improved        |
| 11      | 26     | M   | 58          | 70.4                  | 114.8                 | 1.78           | 5.75           | 0.31           | Cured           |
| 12      | 65     | M   | No          | 62.5                  | No                    | 2.79           | 12.1           | 0.231          | Improved        |
| 13*     | 55     | M   | 77          | 78.8                  | 101.5                 | 4.03           | 7.07           | 0.57           | Improved        |
| 14      | 51     | M   | No          | 73.2                  | No                    | 2.78           | 11.77          | 0.236          | Improved        |
| 15      | 46     | M   | No          | 56                    | No                    | 2.99           | 15.48          | 0.193          | Improved        |
| 16      | 60     | M   | No          | 63                    | No                    | 4.01           | 8.19           | 0.49           | Cured           |
| 17      | 25     | F   | 55          | 50.9                  | 129.1                 | 1.44           | 5.07           | 0.284          | Cured           |
| 18      | 48     | F   | 58          | 61.2                  | 90.6                  | 2.37           | 11.84          | 0.201          | Cured           |
| 19      | 62     | F   | 50          | 64.6                  | 62.7                  | 8.51           | 17.18          | 0.495          | Cured           |
| 20      | 53     | F   | 53          | 40.5                  | 118.3                 | 2.56           | 11.56          | 0.221          | Improved        |
| 21      | 30     | F   | 46          | 37.7                  | 118.6                 | 2.94           | 13.3           | 0.221          | Cured           |
| 22      | 57     | F   | 63          | 69.8                  | 77.8                  | 3.35           | 17.15          | 0.195          | Improved        |

*Mean 52.6 ± 12.1, *SD 24.38 ± 5.36

*positive CSF cultures, patient 2, 3, 4, 7, 9, 13 had one isolate from positive CSF culture each, with *Pneumoniae streptococcus*, *Enterococcus faecium*, *Staphylococcus aureus*, Coagulase-negative *staphylococcus*, *Staphylococcus saprophyticus*, and *Enterococcus hirae*, respectively.
vancomycin dosing including maintenance and loading dose, and administration methods such as intermittent or continuous infusion, different sampling times, and measurement methods of vancomycin concentrations might be explained for variations of vancomycin CSF concentrations in different studies. More importantly, vancomycin penetration into CNS correlates with the level and infectious process of inflammatory meningeal (7). Community acquired meningitis usually resulted in much more prominent damage of the blood brain barrier, which may explain the reason that CSF C\text{min} in this study were clearly lower than that of another studies despite similar serum trough concentrations (16, 17). Moreover, the correlation between vancomycin CSF C\text{min} and serum C\text{min} was similar to other studies (14, 17).

The positive correlation between vancomycin CSF C\text{min} and the decline of WBCs in the CSF after 3-5 days of therapy indicated that higher CSF C\text{min} could be beneficial for improvement of WBCs in CSF. Surprisingly, the study failed to demonstrate an association between vancomycin CSF C\text{min}, serum C\text{min}, CSF to serum C\text{min} ratio and clinical response. This indicates that perhaps monitoring CSF C\text{min} would provide a better monitoring parameter. However, the results showed that higher CSF C\text{min} and CSF to serum C\text{min} ratio could not bring better clinical improvement, which might be related to the decline of subsequent CSF vancomycin concentrations as the BBB becoming more impermeable during prolong therapy (16). Paradoxically, some patients with improved clinical response had clearly low CSF C\text{min}. Patients 11 and 17 had low CSF C\text{min} 1.78 and 1.44 mg/L, respectively, which were far below the vancomycin CSF levels of 3.45 mg/L in inflamed meningitis, but both of them were cured which suggested that these patients may have causative pathogens with high susceptibility to vancomycin or have non-inflamed meningitis. While, patients 10 and 19 were clinically improved despite high CSF C\text{min} (7.17 and 8.51 mg/L). Moreover, patients with similar CSF C\text{min} obtained different clinical response such as patients 5, 6, 7, 8. Due to the negative CSF cultures and unobtainable antimicrobial susceptibility in all but 6 patients, it suggests that more post neurosurgery patients with reliable positive CSF cultures are needed to clarify the association between vancomycin concentrations and clinical response.

Infectious Diseases Society of America (IDSA) guidelines recommended maintaining vancomycin serum C\text{min} between 15 and 20 mg/L for acute bacterial meningitis (18). In this study, 32% (7/22) patients achieved the target level, with widely various CSF C\text{min} (ranging from 2.57 to 8.51 mg/L, mean (±SD) of 3.84±2.09 mg/L). Two patients obtained serum C\text{min} over 20mg/L (patients 6 and 10, with CSF C\text{min} 4.62, 7.17 mg/L respectively) without toxicity. No obvious improvement for clinical response of patients with higher serum C\text{min} (≥15 mg/L) \( (p=0.666) \). More clinical data supporting a serum C\text{min}≥ 15 mg/L for bacterial meningitis are needed. The IDSA recommended a vancomycin dosage of 15-20 mg/kg every 8-12h for acute bacterial meningitis (18). In this study, vancomycin was administrated as the regular regimen (500 mg iv every 6 hours). Also, the lowest patient weight in this study was 46 kg. By using 15 mg/kg/dose, this patient should have received 690 mg at minimum. The results suggest that the dosing regimen used in the hospital may not be the optimal to treat bacterial meningitis.

There was still some limitations for this study. The sample size of the study is small. Also, the inability to obtain reliable positive cultures in the hospital posed difficulties in determining true infection verses false negative cultures. The vancomycin dosing for postsurgical meningitis may not reflect current practice. Since vancomycin concentrations in this study were only obtained once, the relative stability of CSF concentrations during the therapy was unknown.

CONCLUSIONS

There was a positive correlation between serum C\text{min} and CSF C\text{min}. However, only CSF C\text{min} was positively correlated with WBCs improvement. All other parameters such as CSF C\text{min}, serum C\text{min} and CSF to serum C\text{min} ratio had no correlation with clinical response. Future studies with larger sample size are needed to determine the correlation between vancomycin BBB penetration or serum C\text{min} and clinical response.

ACKNOWLEDGEMENTS

This work was supported by all medical workers in the Department of Neurosurgery at the Second Xiangya Hospital of Central South University. The authors would like to thank all patients who participated in this study, and would like to thank Professor Andrew Cave (Faculty of Medicine and Dentistry/Department of Family Medicine, University of Alberta, Edmonton, AB, T5S 1K9,
REFERENCES

1. Wand DX, Wu Q, Tan X, Zeng HY, Zhang ZP. Epidemiology of Intracranial Infection after Craniotomy: A Meta-analysis. West China Med J, 2013; 10:1530-1534.

2. Cui XL, Yu HE, Wang YG, Lin S, Liu LH. Distribution and Antimicrobial Resistance Analysis of Pathogens in CSF of Postoperative CNS Infection. Chin J Pharmacoepidemiol, 2015; 24(01):33-38.

3. Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. Clin Infect Dis, 2006; 42(Suppl.1):S35-S39.

4. Albanese J, Leone M, Bruguerolle B, Ayem ML, Lacarelle B, Martin C. Cerebrospinal fluid penetration and pharmacokinetics of vancomycin administered by continuous infusion to mechanically ventilated patients in an intensive care unit. Amicrob Agents Chemother, 2000; 44(5):1356-1358.

5. Ricard JD, Wolff M, Lacherade JC, Mouvillier B, Hidri N, Bamaud 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(2):250-255.

6. Shokouhi S, Darazam IA. Determination of vancomycin trough level in serum and cerebrospinal fluid of patients with acute community-acquired meningitis: A prospective study. J INFECTION, 2014; 69(5):424-429.

7. Chen K, Wu YX, Wang Q, Wang JQ, Li XG, Zhao ZG, et al. The methodology and pharmacokinetics study of intraventricular administration of vancomycin in patients with intracranial infections after craniotomy. J CRIT CARE, 2015; 30(1):218.e1-e5.

8. Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Michael Scheld W, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis, 2004; 39 (9):1267-1284.

9. Han L, Zhu SJ, Guo YH, Li LY, Hu BJ, Wu YH, et al. Hand Hygiene Compliance in China: An Evaluation. Chinese Journal of Nosocomiology, 2006; 16(2):140-142.

10. Martin JH, Norris R, Barras M, Roberts J, Morris R, Doogue M, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Clin Biochem Rev, 2010; 31(1):21-24.

11. Lodise TP, Lomaestro B, Graves J, Drusano GL. Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. Antimicrob Agents Chemther, 2008; 52(4):1330-1336.

12. Vancomycin, 500mg, powder for solution for infusion (2015). http://www.medicines.org.uk/emc/medicine/25441. Accessed 22 March 2015.

13. Rybak M, Lomaestro B, Rotschafer JC, Moellering RJr, 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 Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm, 2009; 66(1): 90.doi: 10.2146/ajhp080434.

14. Nagl M, Neher C, Hager J, Pfauelder B, Schmutzhard E, Allerberger F. Bactericidal activity of vancomycin in cerebrospinal fluid. Antimicrob Agents Chemother, 1999; 43:1932-1934.

15. Li Y, Lv Y, Xue F, Zhang XZ, Hu YJ, Yu T, et al. Antimicrobial susceptibility surveillance of gram-positive bacterial from Ministry of Health National Antimicrobial Resistant Investigation Net (Mohnarin) 2011-2012. Chin J Clin Pharmacol, 2014; 30(3): 251-260.

16. Viladrich PF, Gudiol F, Linares J, Pallares R, Sabate I, Rifi G, et al. Evaluation of vancomycin for therapy of adult pneumococcal meningitis. Antimicrob Agents Chemother, 1991; 35(12):2467-2472.

17. Visconti EB, Peter G. Vancomycin treatment of cerebrospinal fluid shunt infections. Report of two cases. J Neurosurg, 1979; 51: 245–246.doi: 10.3171/jns.1979.51.2.0245.

18. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant Staphylococcus aureus Infections in Adults and Children. Clin Infect Dis, 2011; 52(3):18-55.doi: 10.1093/cid/cir034.