Abstract

Objective: To evaluate the effect of therapeutic drug monitoring (TDM) of vancomycin in neurosurgery patients.

Methods: In this retrospective, single-center cohort study, data were collected from patients administered vancomycin after neurosurgery during 2020. Intervention by a pharmacist using an area under the curve (AUC)-based strategy for TDM of vancomycin was started on 1 July 2020. The trough concentration was monitored previously. Data regarding basic demographics, vancomycin application, and TDM were collected and analyzed.

Results: Ninety and 155 samples were included in the non-intervention and intervention groups, respectively. No difference in baseline characteristics was detected. After intervention, the attainment rate of vancomycin TDM was significantly increased from 36.7% to 52.3%. The intervention resulted in an increased daily vancomycin dose (28.9 vs. 26.7 mg/kg/day), a more reasonable sample extraction time (sixth vs. ninth dose), reductions in dose adjustments (37.4% vs. 54.4%) and preventative applications (66.7% vs. 52.3%), and no difference in kidney function impact. The intervention group had a shorter hospital stay.

Conclusions: Intervention by a clinical pharmacist using an AUC-based strategy for vancomycin TDM can provide benefits other than pharmacokinetic attainment in neurosurgery patients.
Further prospective multi-center studies are needed to establish standardized intervention measures and evaluation indicators.

**Keywords**
Vancomycin, therapeutic drug monitoring, neurosurgery, trough concentration, area under the curve, pharmaceutical care

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**Introduction**
Vancomycin is one of the most commonly used antibacterial agents after neurosurgery and plays an important role in the prevention and treatment of common postoperative infections in neurosurgery patients. As a drug that has been on the market for more than 60 years, therapeutic drug monitoring (TDM) of vancomycin has been widely performed. The previous guideline\(^1\) recommended monitoring on the basis of the trough concentration. For example, for methicillin-resistant *Staphylococcus aureus* (MRSA) infection, the recommended trough concentration is 10 to 20 mg/L, and the recommended concentration for severe infection is 15 to 20 mg/L. In 2020, the American Society of Health-System Pharmacists, Infectious Diseases Society of America, Pediatric Infectious Diseases Society, and Society of Infectious Diseases Pharmacists issued a new guideline recommending TDM of vancomycin on the basis of the ratio of the area under the curve (AUC) over 24 hours to the minimum inhibitory concentration (AUC/MIC).\(^2\) When the MIC of MRSA is determined to be 1 mg/L using broth microdilution methods, a target AUC between 400 and 600 mg*hour/L is suggested for invasive MRSA infections in adults and children according to the clinical efficacy and safety data. The Chinese Pharmacological Society later issued a new guideline, suggesting that TDM of vancomycin can be based on the trough concentration or AUC/MIC.\(^3\) Although trough concentration monitoring has been implemented in our neurosurgery department for several years, it is still worthwhile to explore new monitoring methods, especially because many studies have reported that the trough concentration of vancomycin often fails to meet the standard among neurosurgery patients.\(^4\)\(^ \text{–}^6\) In addition, surgeons are relatively unfamiliar with AUC-based monitoring and do not know how to perform, calculate, or adjust dosing strategy. Therefore, the pharmacy department of our hospital assigned a clinical pharmacist to perform an antibiotic stewardship program for vancomycin in the neurosurgery department. The purpose of this study is to analyze the effectiveness of TDM of vancomycin before and after intervention by a clinical pharmacist.

**Materials and methods**
This is a retrospective cohort study reported according to the STrengthening the Reporting of OBservational Studies in Epidemiology (STROBE) statement.\(^7\) Because this study is a retrospective analysis, ethical approval was not required. Trough concentration monitoring of vancomycin was recommended but not required...
in the Neurosurgery Department of the First Medical Center of PLA General Hospital, and intervention by a pharmacist was not performed before July 2020. After the publication of new therapeutic monitoring guidelines for vancomycin use in treating serious MRSA infections, a pharmacist was assigned to perform TDM and to calculate the AUC of vancomycin in patients for the neurosurgery department.

Data collection, grouping, and definition
Data were retrospectively collected from patients in the Neurosurgery Department of the First Medical Center of PLA General Hospital who received vancomycin after neurosurgery from January 2020 to December 2020. Data regarding basic demographics, vancomycin application, and TDM were collected and analyzed. Only the first TDM sample of each patient was included. The data were divided into non-intervention and intervention groups according to whether patients received intervention from the pharmacist, and the trough concentration or AUC was used as the evaluation index. The inclusion criteria included use of vancomycin for more than 48 hours and performance of TDM of vancomycin within the course of therapy via trough concentration monitoring or calculation of the AUC on the basis of the trough and peak concentrations. The exclusion criteria included pediatric patients, measurement of the vancomycin trough concentration before the third dose, and missing more than 50% of the data. The Cockcroft–Gault Formula was used to calculate the creatinine clearance rate (CCr), and augmented renal clearance (ARC) was defined as a CCr $\geq 130$ mL/minute. The therapy type was classified as preventative, i.e., no evidence of infection or pathogenic detection; empiric, which referred to infection without pathogenic detection; or targeted, i.e., infection with Gram-positive bacteria. We have de-identified all patient details in this study.

Intervention strategy
Intervention by the pharmacist was performed after prescription of the drug and included suggestions regarding reducing unnecessary preventative medication, optimization of the dose regimen, timely monitoring reminders, AUC calculation, and suggestions regarding dosing adjustment. Attainment of vancomycin TDM was defined as a trough concentration between 10 and 20 mg/L or an AUC between 400 and 600 mg*hour/L. AUC calculation was performed on the basis of trough and peak concentrations using an online tool (vancomycin calculator, https://clincalc.com/vancomycin/).

Outcomes
The primary outcome of this study was the attainment rate of vancomycin TDM. The secondary outcomes included dose rationalization, defined as complying with the recommended dosage of 15 mg/kg q12h; the rate of achieving a reasonable monitoring time, defined as 48 hours after the first dose; the need for therapy adjustment; the incidence of renal impairment, defined as acute renal injury according to the Kidney Disease Improving Global Outcome guideline; and the length of hospital stay.

Statistical analysis
The mean and standard deviation and the median and interquartile range were used to assess normally distributed quantitative variables and skewed variables. The Kruskal–Wallis U test and chi-square or Fisher’s exact test were used, as appropriate, to compare continuous and categorical data, respectively. The relationship between intervention by the pharmacist and the vancomycin TDM attainment rate was
evaluated using a logistic regression model by adjusting for confounding variables, which were selected on the basis of a p value <0.05 in the univariate analysis and clinical relevance. The statistical software package R, version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) was used in all analyses, and a value of p < 0.05 was considered statistically significant.

Results
A total of 251 vancomycin TDM samples were included in this study. The trough concentration was used as a measurement indicator from January 2020 to June 2020. Ninety-six samples were collected during this period, and six samples with more than 50% of data missing were excluded. Ninety samples were included in the non-intervention group. AUC-based vancomycin monitoring was performed from July 2020 to December 2020 after intervention by a pharmacist. A total of 155 samples with no missing data were included in the intervention group (Figure 1). The baseline characteristics of patients are shown in Table 1. No difference was observed in sex, age, height, weight, body mass index, baseline CCr, and ARC rate between the two groups. The total ARC rate of our cohort was 32.2%.

Table 2 shows the vancomycin attainment rate of the two groups, which was defined as a trough concentration between 10 and 20 mg/L in the non-intervention group and an AUC between 400 and 600 mg·hour/L in the intervention group. The intervention group showed a significantly increased attainment rate, 52.3% vs. 36.7%, p = 0.026. The daily dose was higher in the intervention group than in the non-intervention group, 28.9 mg/kg/day vs 26.7 mg/kg/day, p = 0.004. After the intervention, the sample extraction time was reduced to the sixth dose before measurement, compared with the ninth dose in the non-intervention group, p < 0.001. Fewer patients required therapeutic adjustment in the intervention group, 37.4% vs. 54.4%, p = 0.014.

Figure 1. Flow chart of the research.
TDM, therapeutic drug monitoring; AUC, area under the curve.
The empiric and targeted therapy rates were significantly increased in the intervention group, \( p = 0.01 \). The length of hospital stay was shorter in the intervention group, 25 days compared with 22 days in the non-intervention group (\( p = 0.016 \)). The change in renal function before and after vancomycin treatment was not different between the two groups. The attainment rate of vancomycin TDM was associated with intervention by the pharmacist (crude odds ratio 1.89; 95% confidence interval 1.11–3.22 \( p = 0.019 \)). Intervention significantly increased the attainment rate, even after adjusting for possible confounding factors (adjusted odds ratio 2.53; 95% CI 1.31–4.86 \( p = 0.005 \), as shown in Table 3.

**Discussion**

Vancomycin is one of the oldest antibacterial drugs, and TDM of vancomycin has been clinically implemented for many years. Vancomycin has been widely used

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**Table 1.** Baseline characteristics of patients.

| Variables                  | Total (n = 245) | Non-intervention group (n = 90) | Intervention group (n = 155) | p    |
|---------------------------|----------------|-------------------------------|-----------------------------|------|
| Sex. male, n (%)          | 154 (62.9)     | 61 (67.8)                     | 93 (60)                     | 0.281|
| Age, years, median (IQR)  | 52.0 (36.0, 62.0) | 48.0 (35.0, 58.8)             | 53.0 (37.0, 63.0)           | 0.14 |
| Height, cm, median (IQR)  | 170.0 (162.0, 175.0) | 170.0 (165.0, 173.0)          | 170.0 (161.0, 176.0)        | 0.256|
| Weight, kg, median (IQR)  | 70.0 (60.0, 78.0) | 69.0 (60.0, 78.0)             | 70.0 (60.0, 78.0)           | 0.624|
| BMI, median (IQR)         | 24.0 (21.8, 27.0) | 24.3 (22.0, 27.1)             | 23.9 (21.8, 26.9)           | 0.751|
| CCr, mL/minute, median (IQR) | 113.7 (88.9, 143.1) | 115.4 (91.8, 138.9)          | 110.6 (86.2, 143.2)         | 0.591|
| ARC, n (%)                | 79 (32.2)      | 25 (27.8)                     | 54 (34.8)                   | 0.318|

IQR, interquartile range; BMI, body mass index; CCr, creatinine clearance rate; ARC, augmented renal clearance.

**Table 2.** Therapeutic drug monitoring of vancomycin and outcomes of patients.

| Variables                  | Total (n = 245) | Non-intervention group (n = 90) | Intervention group (n = 155) | p    |
|---------------------------|----------------|-------------------------------|-----------------------------|------|
| Attainment, n (%)         | 114 (46.5)     | 33 (36.7)                     | 81 (52.3)                   | 0.026|
| Daily dose mg/kg/day, median (IQR) | 27.8 (23.5, 33.3) | 26.7 (22.6, 32.3)             | 28.9 (25.1, 34.5)           | 0.004|
| Therapy course, days, median (IQR) | 7.0 (4.0, 12.0) | 7.0 (4.0, 13.0)               | 7.0 (4.0, 12.0)             | 0.81 |
| Dose before measurement   | 8.0 (4.0, 12.0) | 9.0 (6.0, 14.0)               | 6.0 (4.0, 10.1)             | <0.001|
| Dose adjustment, n (%)    | 107 (43.7)     | 49 (54.4)                     | 58 (37.4)                   | 0.014|
| Therapy type, n (%)       | 141 (57.6)     | 60 (66.7)                     | 81 (52.3)                   | 0.01 |
| Preventive                | 141 (57.6)     | 60 (66.7)                     | 81 (52.3)                   | 0.014|
| Empiric                   | 55 (22.4)      | 21 (23.3)                     | 34 (21.9)                   |      |
| Targeted                  | 49 (20.0)      | 9 (10)                        | 40 (25.8)                   |      |
| Trough concentration, mg/mL, median (IQR) | 9.9 (6.3, 15.1) | 8.7 (6.3, 14.6)               | 10.0 (6.2, 15.4)            | 0.664|
| SCr before intervention, \( \mu \text{mol}/L \), median (IQR) | 62.6 (49.1, 76.9) | 63.1 (52.8, 76.9)             | 61.2 (46.5, 76.9)           | 0.326|
| SCr after intervention, \( \mu \text{mol}/L \), median (IQR) | 58.6 (47.3, 73.3) | 58.3 (48.3, 72.0)             | 58.9 (46.0, 73.4)           | 0.839|
| LOS, days, median (IQR)   | 23.0 (18.0, 35.0) | 25.0 (20.0, 36.0)             | 22.0 (16.0, 34.5)           | 0.016|

IQR, interquartile range; SCr, serum creatinine; LOS, length of hospital stay.
in neurosurgery patients, and a certain understanding of vancomycin TDM exists among neurosurgeons. However, misunderstandings still exist in clinical practice. After the new guidelines were published in 2020,\textsuperscript{2,3} surgeons had difficulty in understanding and using relatively complicated pharmacokinetic parameters such as the AUC or AUC/MIC. In our study, after intervention by the pharmacist, the attainment rate of vancomycin TDM was significantly increased. Additionally, other advantages included an increased daily vancomycin dose, a more reasonable sample extraction time, the need for fewer adjustments, a reduced proportion of preventative application of vancomycin, and no difference in kidney function impact.

Joaquim F Monteiro reported that the clearance rate of vancomycin was significantly elevated in neurosurgery patients.\textsuperscript{9} Regarding the dosing strategy for vancomycin in neurosurgery patients, its augmented clearance rate should be considered, and TDM should be performed as needed. Similar to a previous report,\textsuperscript{10} in our study, approximately one-third (32.2\%) of patients exhibited ARC. Therefore, the attainment rate of vancomycin TDM in this cohort was only 46.5\%. Another factor that greatly affected vancomycin exposure was the low daily dose, although the dose was increased from 26.7 mg/kg/day to 28.9 mg/kg/day after intervention. This dosage is lower than that recommended by the guideline,\textsuperscript{2} and few surgeons understand the concept of a loading dose, which led to the establishment of 1 g of vancomycin every 12 hours as a universal dose without consideration of the patient’s weight. Compliance with TDM of vancomycin has been a key point of pharmaceutical intervention, but real-world data are not optimistic. Jane E Carland found that suboptimal vancomycin TDM remains a problem despite the availability of local and international guidelines.\textsuperscript{11} Only 24\% of vancomycin courses included in that study involved administration of a loading dose. Additionally, in 72\% of cases, the loading dose was lower than recommended, and in 34\% of cases, the maintenance dose was also lower than recommended. Real vancomycin trough concentrations were extracted in only 14\% of samples, and in more than half, dose adjustment was not implemented. Tatjana Van Der Heggen reported that 68\% of adults, 76\% of children, and 52\% of neonates in their study had sub-therapeutic vancomycin concentrations.\textsuperscript{12} Some patients, especially children and neonates, never reached the target concentrations, even after dose adjustment. The authors also emphasized the importance of vancomycin TDM awareness for all healthcare professionals involved in patient care. However, in our study, intervention by the pharmacist was not allowed before prescription of vancomycin. To address this problem, future studies should focus on interventions performed before a prescription is issued.

Many studies have shown the relationship between the AUC of vancomycin and acute kidney injury\textsuperscript{13} and have shown that AUC monitoring can result in a decreased risk of acute kidney injury compared with trough concentration monitoring.\textsuperscript{14} However, implementation of AUC monitoring is difficult. Wesley D Kufel reported

| Variable                  | Attainment, n (%) | p     |
|---------------------------|-------------------|-------|
| Total                     | 114 (46.5)        |       |
| Non-intervention group    | 33 (36.7)         |       |
| Intervention group        | 81 (52.3)         |       |
| Crude OR 95\% CI          | 1.89 (1.11–3.22)  | 0.019 |
| Adjusted OR 95\% CI       | 2.53 (1.31–4.86)  | 0.005 |

Covariates: all of the variables in Table 1 and Table 2. OR, odds ratio; CI, confidence interval.
that the most common challenge encountered by institutions performing AUC-based monitoring was pharmacist and/or provider unfamiliarity. Additionally, it must be noted that TDM of vancomycin has been the subject of some controversy. Thomas J Dilworth suggested that AUC monitoring for empiric therapy is futile, and a loading dose may decrease the workload of monitoring for broad application. Prospective studies have also found no significant correlation between pharmacokinetic/pharmacodynamic indices and the clinical or microbiological efficacy of vancomycin in Chinese patients. However, considering the severity of post-neurosurgery infection, the prevalence of preventative and empiric treatment because of difficulties in pathogen culture and the risk-benefit balance, and the relative lack of awareness of rational application of vancomycin by neurosurgeons, which is demonstrated by the lack of a loading dose, low dose exposure, and unwillingness to stop treatment, TDM of vancomycin should be used to ensure a therapeutic effect and reduce additional damage. Trough concentration monitoring is an option that is still recommended by the Chinese guideline; however, some hospitals cannot properly perform trough concentration monitoring or, particularly, AUC monitoring. Furthermore, treatment failure has been reported when the trough concentration of vancomycin is within the treatment range but the AUC/MIC fails to meet the target. Thus, it is reasonable to use an AUC-based monitoring strategy with the help of a pharmacist performing pharmacokinetic calculations and interpretation of the results.

In our study, intervention by a pharmacist was performed after prescription of vancomycin and was based on the principle of antimicrobial stewardship. Education and training were performed weekly for doctors, including suggestions about reducing unnecessary preventative medication and the importance of vancomycin concentration monitoring. Dose regimen optimization was performed for every vancomycin prescription, and an electronic record reminder was sent to doctors on the monitoring day. AUC calculation and adjustment suggestions were completed in a timely manner and sent to doctors via the electronic system. Although we did not perform a prospective study, and intervention was not performed before surgeons administered a prescription, the intervention partially achieved the targets of rationalization of the treatment dose and timelier TDM via communication between the pharmacist and surgeons. Required dose adjustments were reduced after intervention by the pharmacist, and the length of the hospital stay was also reduced during the intervention period, although this may not have been solely because of the intervention of the pharmacist. These results demonstrate the necessity of involving clinical pharmacists in TDM of vancomycin.

Limitations
This study has several limitations. First, this is a retrospective cohort study, and therefore, similar to other retrospective analyses, the potential for residual confounding factors may exist. We adjusted as many covariates that may be related to the outcomes as possible. Second, because of the lack of mortality and since more than half of patients were receiving preventative therapy, it was impossible to evaluate the efficacy of vancomycin using indicators of infection. We used the treatment course, rate of need for adjustment, and length of hospital stay as alternative indicators. Finally, this is a single-center study with a relatively small sample size. Further prospective multi-center studies should be conducted to provide additional evidence for clinical decision-making.
Conclusion
Real-world vancomycin application and TDM is not ideal for neurosurgery patients. Intervention by clinical pharmacists using an AUC-based strategy instead of the trough concentration can increase the attainment rate of vancomycin TDM. This method can also promote rationalization of the vancomycin dosage, optimize the monitoring time, reduce requirements for adjustment, decrease preventative application, and shorten the average length of hospital stay.

Declaration of conflicting interest
The authors declare no conflict of interest in preparing this article.

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References
1. Ye Z-K, Chen Y-L, Chen K, et al. Therapeutic drug monitoring of vancomycin: a guideline of the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society. J Antimicrob Chemother 2016; 71: 3020–3025.
2. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Clin Infect Dis 2020; 71: 1361–1364.
3. He N, Su S, Ye Z, et al. Evidence-based Guideline for Therapeutic Drug Monitoring of Vancomycin: 2020 update by the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society. Clin Infect Dis 2020; 71: S363–S371.
4. Kim AJ, Lee J-Y, Choi SA, et al. Comparison of the pharmacokinetics of vancomycin in neurosurgical and non-neurosurgical patients. Int J Antimicrob Agents 2016; 48: 381–387.
5. Wu F-LL, Liu S-S, Yang T-Y, et al. A larger dose of vancomycin is required in adult neurosurgical intensive care unit patients due to augmented clearance. Ther Drug Monit 2015; 37: 609–618.
6. Yao M, Li J, Shi L, et al. Analysis of influencing factors of trough serum vancomycin concentrations in critically ill neurosurgical patients. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2019; 31: 1384–1388.
7. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg 2014; 12: 1495–1499.
8. Cook AM and Hatton-Kolpek J. Augmented renal clearance. Pharmacotherapy 2019; 39: 346–354.
9. Monteiro JF, Hahn SR, Gonçalves J, et al. Vancomycin therapeutic drug monitoring and population pharmacokinetic models in special patient subpopulations. Pharmacol Res Perspect 2018; 6: e00420.
10. Chen Y, Liu L and Zhu M. Effect of augmented renal clearance on the therapeutic drug monitoring of vancomycin in patients after neurosurgery. J Int Med Res 2020; 48: 0300060520949076.
11. Carland JE, Stocker SL, Baysari MT, et al. Are vancomycin dosing guidelines followed? A mixed methods study of vancomycin prescribing practices. Br J Clin Pharmacol 2021; 87: 4221–4229.
12. Van Der Heggen T, Buyle FM, Baysari MT, et al. Vancomycin dosing and therapeutic drug monitoring practices: guidelines versus real-life. Int J Clin Pharm 2021: 43: 1394–1403.
13. Aljefri DM, Avedissian SN, Rhodes NJ, et al. Vancomycin area under the curve and acute kidney injury: a meta-analysis. Clin Infect Dis 2019; 69: 1881–1887.
14. Oda K, Jono H, Nosaka K, et al. Reduced nephrotoxicity with vancomycin therapeutic drug monitoring guided by area under the concentration–time curve against a trough 15–20 μg/mL concentration. *Int J Antimicrob Agents* 2020; 56: 106109.

15. Kufel WD, Seabury RW, Mogle BT, et al. Readiness to implement vancomycin monitoring based on area under the concentration–time curve: a cross-sectional survey of a national health consortium. *Am J Health Syst Pharm* 2019; 76: 889–894.

16. Dilworth TJ, Schulz LT and Rose WE. Vancomycin advanced therapeutic drug monitoring: exercise in futility or virtuous endeavor to improve drug efficacy and safety? *Clin Infect Dis* 2021; 72: e675–e681.

17. Liang X, Fan Y, Yang M, et al. A prospective multicenter clinical observational study on vancomycin efficiency and safety with therapeutic drug monitoring. *Clin Infect Dis* 2018; 67: S249–S255.

18. Shen K, Yang M, Fan Y, et al. Model-based evaluation of the clinical and microbiological efficacy of vancomycin: a prospective study of Chinese adult in-house patients. *Clin Infect Dis* 2018; 67: S256–S262.

19. Fu X, Lin Z, Chen S, et al. Treatment of intracranial infection caused by methicillin-resistant *Staphylococcus epidermidis* with linezolid following poor outcome of vancomycin therapy: a case report and literature review. *Infect Drug Resist* 2021; 14: 2533.

20. Cusumano JA, Klinker KP, Huttner A, et al. Towards precision medicine: therapeutic drug monitoring-guided dosing of vancomycin and β-lactam antibiotics to maximize effectiveness and minimize toxicity. *Am J Health Syst Pharm* 2020; 77: 1104–1112.

21. Dyar OJ, Huttner B, Schouten J, et al. ESGAP (ESCMID Study Group for Antimicrobial stewardshipP). What is antimicrobial stewardship? *Clin Microbiol Infect* 2017; 23: 793–798.