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ORIGINAL RESEARCH

Population Pharmacokinetics and Cerebrospinal Fluid Penetration of Intravenous Vancomycin in Intracranial Hemorrhage Patients with External Ventricular Drains: Implications for Dosing and Therapeutic Drug Monitoring

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Purpose: Vancomycin is frequently used to treat central nervous system (CNS) infections, yet its cerebrospinal fluid (CSF) penetration remains poorly characterized in patients with intracranial hemorrhage (ICH) requiring external ventricular drains (EVDs).
Methods: A prospective observational study was conducted on nine neurosurgical patients with ICH and EVDs receiving intravenous vancomycin. Plasma and CSF samples were collected at predefined time points and analyzed by validated assays. Noncompartmental analysis, regression modeling, and nonlinear mixed-effects pharmacokinetic (PK) modeling were performed.
Results: The $AUC_{CSF/plasma}$ ratios ranged from 0.84% to 14.22%. CSF penetration correlated strongly with plasma–CSF concentration ratios at the end of infusion (Spearman r = 0.791; p = 0.004). Linear regression identified urine output (R^2 = 0.51, p = 0.014), WBC/total cell ratio (R^2 = 0.62, p = 0.007), and end-of-infusion concentration (R^2 = 0.45, p = 0.049) as significant predictors of AUC_{CSF}. A two-compartment model provided the best fit for vancomycin population PK, yielding clearance and volume of distribution estimates similar to previous reports, although no significant covariates for CSF penetration were identified.
Conclusion: To our knowledge, this is the first study reporting real-world data of vancomycin CSF penetration in Taiwanese neurosurgical patients. These findings provide a critical PK foundation for developing future model-informed precision dosing strategies and validating surrogate TDM markers in this neurocritical care population.
Keywords: cerebrospinal fluid, external ventricular drain, intracranial hemorrhage, population pharmacokinetics, therapeutic drug monitoring, vancomycin

Introduction

Intracranial hemorrhage (ICH) is a critical medical condition frequently associated with acute hydrocephalus, often necessitating the use of external ventricular drains (EVD) to manage elevated intracranial pressure and cerebrospinal fluid (CSF) diversion. While EVDs are indispensable in these scenarios, they come with a significant risk of ventriculostomy-associated infections (VAI), a severe complication that demands prompt and effective antimicrobial therapy.

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Among the antibiotics used to manage such infections, vancomycin remains a cornerstone due to its potent activity against Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA).

The bactericidal activity of vancomycin and safety correlated with the area under the plasma concentration-time curve over 24 hours to minimum inhibitory concentration (AUC/MIC) ratio. However, a fundamental challenge in central nervous system (CNS) infections is the variation between plasma-based pharmacokinetic (PK) targets and actual drug exposure at the site of infection within the CSF. Achieving therapeutic concentrations of vancomycin in the CSF is particularly challenging. The blood-brain barrier (BBB) and blood-CSF barrier (BCSFB), which regulate drug penetration into the CNS, significantly limit the efficacy of systemic antibiotics. In the setting of meningeal inflammation, the permeability of these barriers may increase, but the extent of this enhancement remains variable and unpredictable.[1] This variability complicates the optimization of dosing regimens in these patients. Subtherapeutic CSF concentrations, potentially due to augmented clearance, can lead to treatment failure.[2] On the other hand, excessive plasma levels increase the risk of systemic toxicity, particularly nephrotoxicity.

Although vancomycin PK data in patients with ventricular-associated infections secondary to ICH with EVDs remain limited, existing research has primarily focused on the CNS penetration of antibiotics, particularly in bacterial meningitis or healthcare-associated ventriculitis.[3–5] However, evidence suggests that during ventriculitis, the meninges may remain in a normal state or exhibit only mild inflammation, which could reduce the effectiveness of antibiotic dosing strategies designed for meningitis.[6] Additionally, there is no definitive clinical evidence confirming that meningitis treatment regimens achieve comparable therapeutic concentrations in the CSF of patients with ventriculitis.[7] Recent studies have begun to provide real-world data specific to neurosurgical populations, highlighting how altered CSF dynamics, the presence of EVDs, and variability in renal function can all influence drug PK.[8]

We therefore hypothesized that vancomycin CSF penetration in patients with ICH and EVDs is limited and highly variable, and that specific clinical or PK factors may partially explain this variability. Current treatment recommendations for MRSA infections, such as those proposed by the IDSA guideline, define therapeutic targets based on plasma AUC/MIC (400–600); however, these targets were not established in populations with meningitis or ventriculitis. As a result, whether plasma-based PK targets adequately reflect CSF exposure and clinical efficacy in neurocritical care patients remains uncertain. In this context, model-informed precision dosing (MIPD) represents a rational approach to bridge this knowledge gap by integrating patient-specific factors to support individualized dosing strategies in this high-risk population.[9] Thus, this study aimed to further investigate the CSF penetration of vancomycin in patients with ICH and EVDs who were undergoing treatment for VAI, while also characterizing the PK parameters in this specific population.

Method

Study Design

This prospective observational study was conducted to evaluate the CSF penetration of vancomycin in adult patients with ICH managed with EVDs. Patient enrollment was carried out from January 2023 to December 2024 at two medical centers in northern Taiwan. Ethical approval was obtained from the National Taiwan University Hospital Research Ethics Committee (202302126RINA). Adult patients aged 20 years or older who were diagnosed with ICH, required EVD placement, and received intravenous vancomycin therapy were included in the study. Informed consent was obtained from all participants or their legal representatives prior to enrollment. Patients were excluded if they had a history of metastatic or intracranial tumors, prior cranial radiation, craniotomy, or ongoing immunosuppressive therapy.

Each patient's initial vancomycin dosing regimen followed the National Taiwan University Hospital protocol, which considers renal function and body weight.[9,10] The loading dose ranged from 20 to 25 mg/kg, with a higher dose of 25 mg/kg recommended for critically ill patients or those with end-stage renal disease (ESRD), capped at a maximum of 3000 mg per dose. Table 1 outlines the empirical maintenance dosing strategy, which is calculated based on a target AUC/ MIC ratio of 400–600 and institutional consensus.

The primary objective of this study was to evaluate the CSF penetration of vancomycin in patients with ICH. The secondary objectives were threefold: (1) to assess potential correlations between demographic characteristics and the $AUC_{CSF/plasma}$ ratio using linear regression analysis; (2) to examine the relationship between single time-point

Table 1 NTUH AUC Based Initial Vancomycin Dosing Nomogram for Adults

CLCr (mL/min)	≦30 kg	40 kg	50 kg	60 kg	≧70–100 kg
100–120	500 mg q8h	500 mg q8h	750 mg q8h	1000 mg q8h	1000 mg q8h
80–100	500 mg q12h	750 mg q12h	1000 mg q12h	1000 mg q12h	1250 mg q12h
60–80	500 mg q12h	500 mg q12h	750 mg q12h	1000 mg q12h	1000 mg q12h
40–60	250 mg q12h	500 mg q12h	500 mg q12h	500 mg q12h	750 mg q12h
20–40	500 mg qd	500 mg qd	750 mg qd	1000 mg qd	1000 mg qd
10–20	250 mg qod	500 mg qod	500 mg qod	500 mg qod	750 mg qod
0–10	250 mg qod	250 mg qod	500 mg qod	500 mg qod	500 mg qod

Notes: Actual body weight used for obese patients; CLcr: creatinine clearance, (140-age) x BW/ (72 x SCr), a SCr of less than or equal to 0.8 mg/dL is automatically input as 0.8 mg/dL.

concentration ratios and the $AUC_{CSF/plasma}$ ratio as a measure of overall antibiotic exposure; and (3) to perform a PK analysis of vancomycin parameters, including clearance (CL) and volume of distribution (Vd), to determine their influence on the AUC ratio. Population PK (popPK) modeling was applied to further elucidate the factors affecting vancomycin's therapeutic efficacy in this high-risk population.

Data Collection

Demographic and clinical characteristics, including age, sex, height, and weight were recorded. Laboratory evaluations were conducted at baseline and two weeks after enrollment, including renal function tests (serum creatinine), high-sensitivity C-reactive protein (hsCRP), complete blood count, CSF analysis, and microbiological culture results. Physiological parameters, such as daily urine output and EVD drainage were also documented.

The diagnosis of meningitis and ventriculitis was based on predefined operational criteria. Meningitis and ventriculitis were diagnosed if a positive culture result obtained in the CSF. Furthermore, meningitis and ventriculitis were suspected if the culture was negative, yet at least one of the following criteria was met: contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) showing ventricular wall enhancement, or CSF analysis indicating turbidity, CSF glucose concentration lower than 50% of blood glucose, protein concentration exceeding 50 mg/dL, pleocytosis, and a cell index greater than 20. Given the diagnostic difficulty in differentiating infectious ventriculitis from sterile inflammation following intraventricular hemorrhage (IVH), particularly in patients with EVDs, these criteria were informed by prior literature highlighting the limitations of conventional CSF markers and the potential utility of the cell index in this setting.[11]

$$Cell\ index = \frac{leukocytes\,(CSF) \div erythrocytes\,(CSF)}{leukocytes\,(blood) \div erythrocytes\,(blood)}$$

Sampling Protocol

Blood and CSF samples were collected from pre-existing central venous or arterial lines and EVDs to minimize additional invasive procedures. Sampling was performed after the fourth dose to approximate steady-state conditions. Give the reported elimination half-life of vancomycin in adult patients (approximately 4–6 hours), steady state is expected to be achieved after 4–5 half-lives, and sampling after the fourth dose is therefore considered reasonable.[12] This timing also reflects standard therapeutic drug monitoring (TDM) practice at our institution. For each patient, 3 mL of blood and 1 mL of CSF were collected at five specific time points during the fifth dosing interval: pre-dose (0 hours), at the end of infusion (C_{end}), and post-dose at 4, 6 and 8 hours. Immediately after collection, all samples were centrifuged and stored at −20°C until further analysis. Plasma vancomycin concentrations were quantified using a validated LC–MS/MS method with a linear calibration range of 0.78–100 μg/mL ($R^2 > 0.99$). Intra- and inter-day precision and accuracy were evaluated at two quality control levels, and all values were within ±15% relative standard deviation. All measurements were performed by the Forensic and Clinical Toxicology Center (FCTC), National Taiwan University.

Statistical Analysis

All statistical analyses were conducted using Microsoft Excel 2024 Ver. 16.91 and Phoenix WinNonlin version 8.5. Descriptive statistics were used to summarize patient demographics and baseline characteristics. Vancomycin PK parameters, including CL, Vd, and AUC-time curve, were estimated. The AUC-time curves from 0 to 24 hours for plasma and CSF were determined using the linear-log trapezoidal method.

The CSF/plasma penetration ratio was assessed at multiple time points, including pre-dose, C_{end}, middle of the dosing interval, and the end of the dosing interval. Spearman correlation analysis was performed to evaluate the relationship between these ratios and the CSF/plasma AUC-time curve ratio. Univariate and multivariate linear regression analyses were performed to assess the effects of different factors on AUC levels. Variables with a univariate regression p-value < 0.15 were considered as candidates for inclusion in the multivariate linear regression model. Correlation coefficients and statistical significance were calculated using R Studio version 4.4.2 (Boston, MA) and Python version 3.10. Scatter plots and regression analyses were generated in both R and Python to visualize these relationships.

PopPK modeling was performed in two stages. First, a base model is constructed to evaluate one-, two-, and three-compartment models. Next, different residual error models (additive, multiplicative, and combined) will be utilized for selection of the optimal model based on statistical criteria. Covariate analysis was conducted using stepwise shotgun covariate search to assess the influence of clinical factors, including age, sex, disease state, CL_{cr}, eGFR, culture results, CSF WBC, CSF glucose level, CSF total protein, cell-index, drainage output, and urine output levels, on vancomycin CL and Vd. Statistical significance was defined as a decrease in objective function value (OFV) by 3.84 (p-value < 0.05) for forward addition and an increase in OFV by 6.63 (p-value < 0.01).

Model evaluation was performed for the final model using diagnostic plots, including observed versus predicted concentrations, weighted residuals versus predicted concentrations, and conditional weighted residuals versus time after dose. The structural model and residual error model were assessed based on these plots, with an evaluation of whether observed trends deviated significantly from model predictions.

Results

Patient Demographics

A total of nine patients were included, with a median age of 67 years and 88.9% being male. The primary indications for EVD placement were intracerebral hemorrhage (66.7%) and subarachnoid hemorrhage (33.3%). Two patients (22.2%) were diagnosed with meningitis/ventriculitis, while an additional seven (77.8%) were suspected cases. The median CL_{cr} was 82.4 mL/min, with mean WBC and CRP levels of 8.29 K/μL and 2.31 mg/dL, respectively. Most patients (88.9%) adhered to the vancomycin dosing protocol, receiving daily doses ranging from 1000 to 3000 mg, all initiated with appropriate loading dose. Detailed demographic and clinical characteristics of the study population are summarized in Table 2.

Table 2 Patient Characteristics

	Total of 9 Patients [a]
Age (y/o)	67 (18)
Male	8 (88.9%)
Body height (cm)	163 (15.375)
Body weight (kg)	71.2 (11.2)
Renal function (CL_{cr}: mL/min)	82.4 (23.9)
EVD indication	
Intracerebral hemorrhage	6 (66.7%)
Subarachnoid hemorrhage	3 (33.3%)

(*Continued*)

Table 2 (Continued).

	Total of 9 Patients [a]
Diagnosis of meningitis/ventriculitis	2 (22.2%)
Meningitis/ventriculitis suspected	7 (77.8%)
Lumbar drainage	1 (11.1%)
Patients adhering to vancomycin protocol dosing	8[b] (88.9%)
WBC (K/μL)	8.29 (1.31)
CRP (mg/dL)	2.31 (2.69)

Notes: CL_{cr}: creatinine clearance, (140-age) x BW/ (72 x SCr), a SCr of less than or equal to 0.8 mg/dL is automatically input as 0.8 mg/dL; [a]Median value (IQR) or percentage. [b]One patient was underdosed according to the recommended vancomycin dosing protocol.
Abbreviations: CRP, C-reactive protein; EVD, external ventricular drain; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage; WBC, white blood count.

PK Analysis

Vancomycin concentration-time profiles were analyzed from blood and CSF samples collected at predefined time points (Figure 1). The median vancomycin trough concentration in plasma was 10.79 μg/mL (IQR: 7.79 μg/mL), while the corresponding CSF concentration was 1.68 μg/mL (IQR: 1.28 μg/mL). AUC was calculated using a linear log trapezoidal approach, yielding a median AUC_{0-24} of 478.10 mg·hr/L (IQR: 199.57 mg·hr/L) and for plasma and a median AUC from first observation to last observation point of 10.29 mg·hr/L (IQR: 9.64 mg·h/L) for CSF. Further details regarding vancomycin CSF penetration and PK parameters data can be seen in Table 3.

The ranges of CSF/plasma penetration ratio was 0.84–14.22%, including data from five right EVDs and six left EVDs. The CSF/plasma concentration ratio showed good correlation with $AUC_{CSF/plasma}$ at predose, C_{end}, middle of the

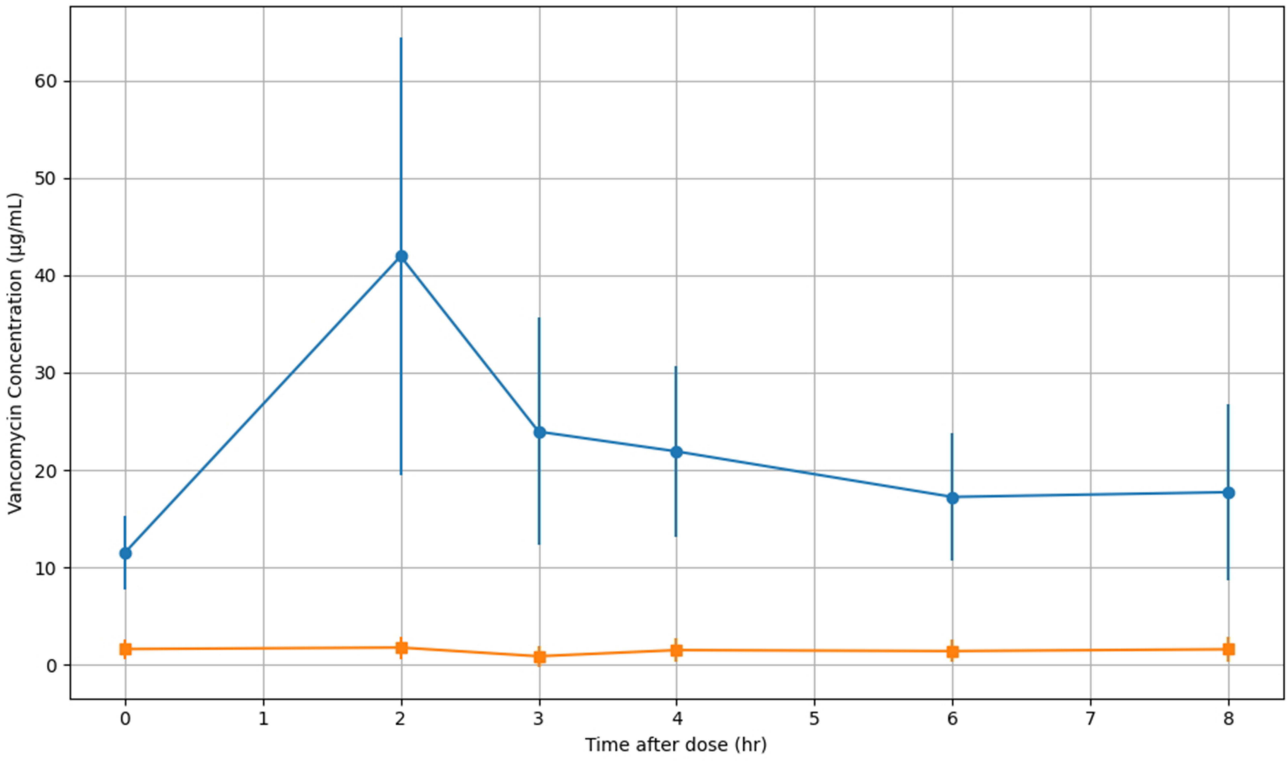

Figure 1 Mean plasma and CSF concentration–time profiles of vancomycin after intravenous administration.
Note: The figure shows the mean vancomycin concentrations in plasma (blue circles) and CSF (orange squares) at predefined sampling time points after dosing (0, 2, 3, 4, 6, and 8 hours). Data are presented as mean ± standard deviation.

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Table 3 Vancomycin CSF Penetration and Individualized Patient PK Parameters Data

Subject	PK Parameters							
	Vd (L)	CL (L/hr)	Plasma C_{trough} (μg/mL)	Plasma AUC_{0-24} (mg*hr/L)	AUC_{Plasma} (mg*hr/L)[a]	AUC_{CSF} (mg*hr/L)[a]	$AUC_{CSF/plasma}$ (%)	CSF Culture
VAN-01	41.98	4.63	8.77	432.28	169.24	(L) 13.64 (R) 13.93	(L) 8.06 (R) 8.23	*Enterococcus faecium*
VAN-02	42.7	6.17	9.24	323.72	128.42	14.17	11.03	–
VAN–03	85.58	2.87	17.92	523.29	166.82	(L) 6.34 (R) 7.7	(L) 3.8 (R) 4.62	–
VAN–04	27.22	4.65	16.56	645.06	215.02	1.81	0.84	–
VAN–05	109.01	3.46	6.99	288.99	104.01	2.48	2.39	–
VAN–06	50.46	13.81	5.42	217.11	72.37	10.29	14.22	–
VAN–07	64.99	4.18	10.79	478.1	186.97	19.26	10.3	*Serratia marescens*
VAN–08	10.04	2.91	17.41	942.73	367.31	30.69	8.36	–
VAN–09	71.68	4.83	11.31	520.42	194.79	2.435	1.25	–
Median (IQR)	50.46 (29.7)	4.63 (1.37)	10.79 (9.24)	478.1 (199.57)	169.2 (66.37)	10.29 (9.64)	8.1 (6.24)	

Note: [a]Defined as the hemorrhage day to the day of sampling.
Abbreviations: AUC, area under the curve; CL, clearance; CSF, cerebrospinal fluid; IQR, interquartile range; Vd, volume of distribution; WBC, white blood cell count.

dosing interval, C4, C6, and C8, with the strongest associations observed at the C_{end} and the middle of the dosing interval (Spearman correlation = 0.791, 0.773; p-value = 0.004, 0.005, respectively). Figure 2 depicts the Spearman correlation plots for these time point ratios.

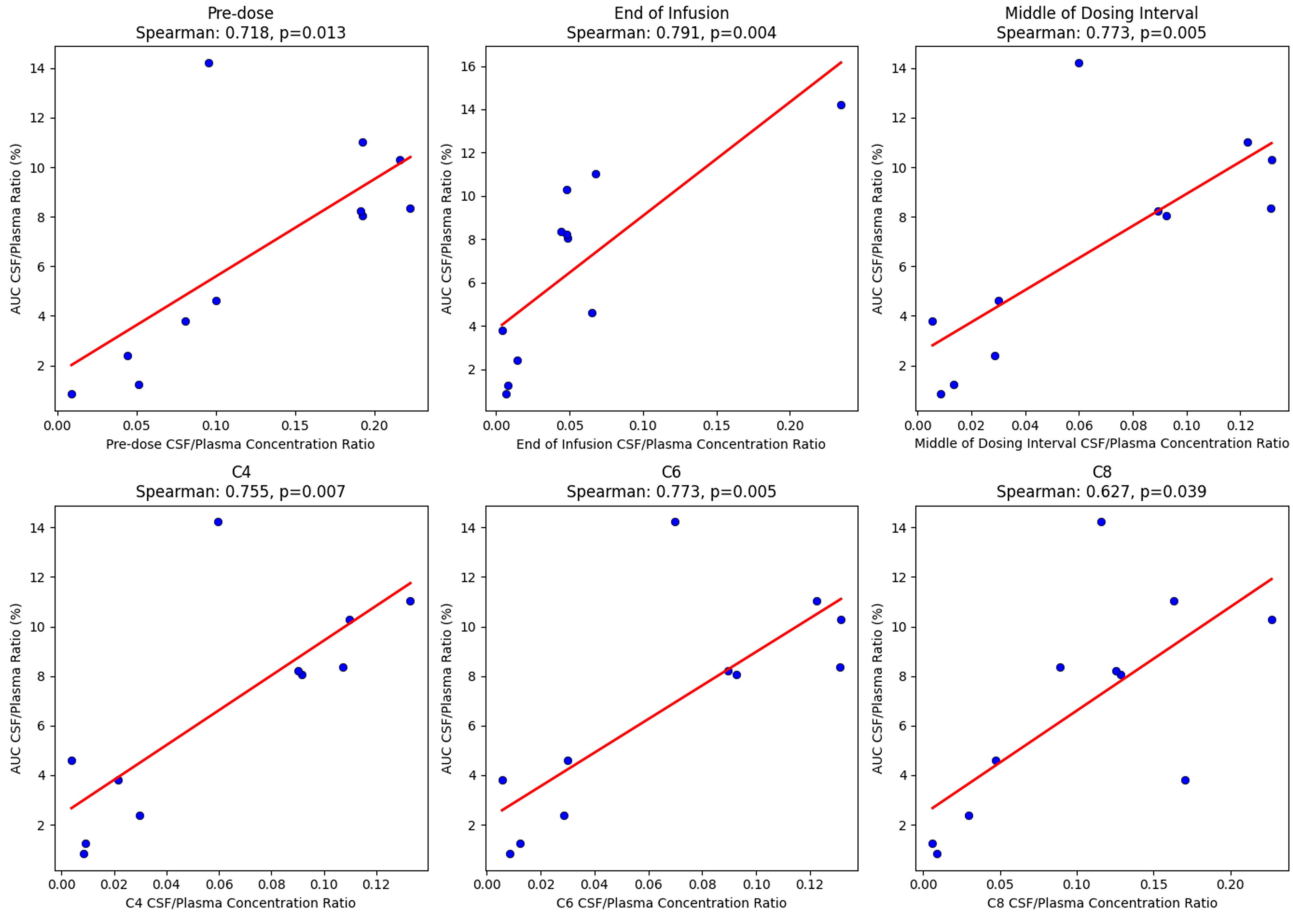

Figure 2 Spearman correlation between single time-point CSF/plasma concentration ratios and overall vancomycin CSF exposure.
Notes: Scatter plots show the relationship between $AUC_{CSF/plasma}$ ratios (%) and CSF/plasma concentration ratios measured at different sampling time points: pre-dose (C0), C_{end}, middle of dosing interval, 4 hours (C4), 6 hours (C6), and 8 hours (C8) after dosing. Spearman correlation coefficients (r) and corresponding p-values are displayed in each panel. Red lines represent linear regression trend lines for visualization purposes. The strongest correlation was observed at C_{end}, suggesting that this single time-point ratio may serve as a practical surrogate marker for estimating overall CSF exposure relative to plasma.

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The median vancomycin Vd was 50.5 L (IQR: 29.7 L), while the CL was estimated at 4.63 L/hr (IQR: 1.37 L/hr). Individual variations in CL were observed, particularly in patients with differing renal function.

Linear Regression

Linear regression analyses between AUC_{plasma}, AUC_{CSF}, and $AUC_{CSF/plasma}$ ratios, and clinical variables (Supplementary Table S1) revealed that urine output, WBC/total cell count (with one outlier removed), and C_{end} were significantly associated with AUC_{CSF}, with regression equations of $AUC_{CSF} = -5.084 \times$ (urine output) + 29.089 ($R^2 = 0.510$, $p = 0.0136$), $AUC_{CSF} = 0.904 \times$ (WBC/total cell) + 8.284 ($R^2 = 0.618$, $p = 0.007$), and $AUC_{CSF} = 0.290 \times C_{end} + 0.253$ ($R^2 = 0.446$, $p = 0.0493$). The multivariate linear regression model for predicting AUC_{CSF} demonstrated $AUC_{CSF} = 18.76–3.997 \times$ (urine output) $– 0.207 \times (C_{end}) + 0.074 \times AUC_{plasma}$, achieving an R^2 of 0.950 with all predictors showing statistical significance ($p < 0.020$).

PopPK Modeling

PopPK modeling was initially conducted using Phoenix NLME software with the First-Order Conditional Estimation with Extended Least Squares (FOCE-ELS) algorithm. One-, two-, and three-compartment infusion models were evaluated (Supplementary Table S2). A two-compartment model with a multiplicative residual error structure was selected as the best fit. The OFV for this model were: LogLik = –137.195, –2LL = 274.391, AIC = 292.391, BIC = 308.651, nParm = 9. The fixed- and random-effect estimates are summarized in Table 4. Since both ωV and ωV2 exhibited shrinkage values greater than 0.9, these random effects were excluded from the final model.

To investigate potential covariates influencing vancomycin PK, patient-specific factors including age, sex, disease state, CL_{cr}, eGFR, culture results, CSF WBC, CSF glucose level, CSF total protein, cell-index, drainage output, and urine output levels were incorporated into the model. However, none of these variables demonstrated a statistically significant impact on Vd or CL ($p \leq 0.05$).

Finally, the final model was established with the following OFV: LogLik = –137.185, –2LL = 274.370, AIC = 288.370, BIC = 301.017, nParm = 7, EPS shrinkage = 0.130, Condition = 23.800. Validation was also performed through bootstrap analysis and visual predictive checks. The parameter estimates for this model and bootstrap results are presented in Table 5, and the visual predictive check and GOF plots are provided in Supplementary Figures S1 and S2.

Table 4 Two-Compartment FOCE-ELS with Multiplicative Residual Error Model Estimates and Parameters

	Parameter	Estimate	Units	Stderr	CV%	2.5% CI	97.5% CI	Shrinkage
Fixed Effect	tvV	6.085	L	1.422	23.371	3.201	8.969	
	tvV2	45.117	L	8.184	18.140	28.519	61.714	
	tvCL	4.288	L/hr	0.652	15.209	2.965	5.610	
	tvCL2	20.157	L/hr	7.054	34.994	5.852	34.463	
	stdev()	0.164		0.014	8.621	0.135	0.193	
Random Effect	ωV	0.011	L	0.006	58.161			0.937
	ωCL	0.188	L	0.116	61.622			0.020
	ωV2	0.000	L/hr	0.000	20.296			0.980
	ωCL2	0.791	L/hr	0.406	51.325			0.181

Abbreviations: CI, confidence interval; CL, clearance; CV, coefficient of variation; Stderr, standard error; Stdev, standard deviation; V, volume of distribution.

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Table 5 Final Model of a Two-Compartment FOCE-ELS with Multiplicative Residual Error Model Estimates and Parameters

	Parameter	Estimate	Units	Stderr	CV%	Median	2.5% CI	97.5% CI	Shrinkage
Final Model	tvV	6.065	L	1.409	23.234		3.212	8.918	
	tvV2	45.117	L	8.232	18.222		28.512	61.843	
	tvCL	4.289	L/hr	0.656	15.297		2.960	5.617	
	tvCL2	20.208	L/hr	7.274	35.995		5.483	34.932	
	stdev()	0.164		0.014	8.594		0.136	0.193	
	ωCL	0.188	L/hr	0.118	62.649				0.020
	ωCL2	0.796	L/hr	0.394	49.436				0.183
Bootstrap	tvV		L			6.080	0.009	19.579	
	tvV2		L			46.929	32.462	265.621	
	tvCL		L/hr			4.239	0.362	6.011	
	tvCL2		L/hr			18.031	8.673	46.945	
	stdev()					0.159	0.118	0.198	
	ωCL		L/hr			0.171	0.012	2.043	
	ωCL2		L/hr			0.624	0.000	2.759	

Abbreviations: CI, confidence interval; CL, clearance; CV, coefficient of variation; Stderr, standard error; Stdev, standard deviation; V, volume of distribution.

Discussion

From our study results, the ranges of $AUC_{CSF/plasma}$ were 0.84–14.22% in ICH patients. Past studies have reported varied vancomycin $AUC_{CSF/plasma}$ ratios ranging from 0–40% (Table 6).[1,3,6,8,13] However, in this study, our patients exhibited a significantly lower range, suggesting reduced vancomycin penetration into the CSF in this cohort.

Despite its widespread use as first-line therapy for Gram-positive CNS infections, a key drawback of vancomycin in patients with ICH is the difficulty in achieving adequate and predictable CSF exposure using standard systemic dosing. Although the BBB and BCSFB are often disrupted after intracranial injury, this does not necessarily translate into increased vancomycin penetration. Several factors may explain this discrepancy. First, the disruption is typically heterogeneous, and changes in active efflux transporters, such as P-glycoprotein and MRPs, or drug metabolism may further limit CSF entry.[14,15] Second, vancomycin is a large, hydrophilic molecule, and its physicochemical properties inherently restrict passive diffusion across the barrier.[16–18] Third, local changes in tissue pH levels within the injured region may alter the drug's ionization state, further reducing its ability to penetrate into the CSF. Fourth, alterations in CSF dynamics, including increased drainage or accelerated flow, can rapidly remove vancomycin from the CSF, resulting in lower measured concentrations and potentially underestimating its true penetration.[19] Finally, clinical observations remain inconsistent: in some infectious or inflammatory settings, BBB disruption has been associated with increased CSF antibiotic levels, whereas in non-infectious conditions such as stroke or ICH, the effects appear to be highly drug- and lesion-specific.[20] Collectively, these factors potentially explain why barrier disruption alone does not reliably predict CSF exposure, and why reliance on plasma-based targets may result in subtherapeutic CSF concentrations despite apparently adequate systemic exposure.

PopPK model was developed using the FOCE-ELS algorithm with a multiplicative residual error structure, and a two-compartment infusion model was selected based on a −2LL of 274.370. While the random effects for CL showed higher variability, the fixed-effect parameter estimates had CV% values below 36%, and the EPS shrinkage was less than 0.30, supporting a stable and reliable model fit. No significant covariates were identified, which may be explained by the predominant influence of renal function that had already been accounted for through the NTUH dosing protocol. Interindividual variability in vancomycin PK was not significantly influenced by common clinical parameters within this cohort. A small population and narrow range of lab data values may also contribute to this result. Previous studies have reported substantial variability in vancomycin popPK models, with different compartmental structures fitting best

Table 6 Previous Studies Comparison of Vancomycin CSF Penetration

Study	Population	Dosing	Sample Points	AUC_{plasma}	AUC_{CSF}	$AUC_{CSF/serum}$	Key Findings
Fan et al, 2022[6]	Post craniotomy (n=22)	1000 mgQ12H IV	C_{trough}, C1, C2, C3, C8	319.4 ± 69.3 mg·hr/L	96.6 ± 67.5 mg·hr/L (infection)	33.2% ± 19.3%	CSF AUC predicted by serum trough + CSF WBCs/total cells
Tuon et al, 2021[8]	Nosocomial ventriculitis (n=33)	30 mg/kg LD, 60 mg/kg/day CI	Not reported (at least 48hr after initial dose)	838 (518~1010) mg·hr/L (median)	Not reported (median = 5.2 mg/L)	8.4–41.5%	CSF/serum correlated with creatinine: 21% AKI
Blassman et al, 2019[3]	Ventriculitis (n=21)	Varied (median = 2500 mg/day Q12H)	C_{trough}, $C_{end}/C_{after\ 4h}$	455.1 mg·hr/L (median)	14.1 mg·hr/L (median)	1-18%	High intersubject variability: low penetration
Shokouhi et al, 2014[13]	Community-acquired meningitis (n=27)	15 mg/kg LD, 30 mg/kg/day Q12H	C_{trough}	Not reported (trough ~ 13.8 mg/L)	Not reported (trough ~ 11.2 mg/L)	81% ± 8%	CSF/serum levels stable over time; strong correlation (r=0.60–0.71)
Beach et al, 2017[1]	Systematic review (13 studies)	Varied	Varied	Varied	Varied	0–81%	Penetration highly variable; not predictive of outcome
Our Study	Post ICH (n=9)	Varied (NTUH dosing protocol)	C0, C_{end}, C4, C6, C8	478.10 mg·hr/L (median)	10.29 mg·hr/L (median)	0.84–14.22%	CSF AUC predicted by daily urine output + C_{end} +AUC_{plasma}

Abbreviations: AKI, acute kidney injury; AUC, area under the curve; C_{end}, end of infusion concentration; CI, continuous infusion; CSF, cerebral spinal fluid; ICH, intracranial hemorrhage; LD, loading dose; Q12H, every 12 hours; WBC, white blood cell count.

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across cohorts.[21–23] Nevertheless, our estimates of Vd and CL were generally comparable to those reported in prior investigations. Future studies should explore alternative modeling approaches and larger datasets to confirm these findings.

Although a validated CSF pharmacodynamic target has not been established, limited clinical data provide a useful exploratory context. Fan et al[6] reported $AUC_{CSF0–24}$/MIC values ranging from 72.90 to 196.00 (median, 125.07) among a small number of cases with Gram-positive pathogens and available MIC data. The authors speculated that maintaining CSF vancomycin concentrations of approximately 4 μg/mL might be adequate; however, this estimate was not prospectively validated and should not be interpreted as a definitive therapeutic target. In conjunction with our findings, in selected high-risk patients, such as those with persistent or recurrent microbiological positivity despite systemic therapy, the end-of-infusion CSF/plasma concentration ratio, together with plasma exposure, may may serve as a pragmatic clinical reference to contextualize whether CSF vancomycin exposure is likely to fall within previously reported ranges (approximately 70–200). Importantly, this approach is intended to provide supportive clinical insight rather than prescriptive guidance, and to facilitate individualized, MIPD rather than to define a rigid CSF target.

From a therapeutic perspective, the low and significantly variable CSF penetration observed in this study raised important concerns regarding the probability of target attainment against common Gram-positive CNS pathogens. Even when plasma AUC/MIC targets are achieved, inadequate CSF exposure may result in subtherapeutic concentrations at the site of infection, particularly for organisms with higher MICs. In this context, earlier consideration of intraventricular administration may be warranted in selected high-risk patients with ICH and EVDs, especially in cases of poor clinical response. Alternative systemic strategies may also be considered, including higher vancomycin dosing with careful toxicity monitoring, or switching to agents with more favorable CNS penetration profiles, such as linezolid, depending on pathogen susceptibility and clinical status.

Beyond immediate clinical decision-making, our findings highlight the potential role of MIPD approaches in optimizing therapy for this population. A robust popPK model combined with limited CSF and plasma sampling, could enable Bayesian forecasting to individualize dosing and identify patients at risk of inadequate CNS exposure. Such an approach may ultimately support the development of practical treatment algorithms, for example, using early CSF/plasma ratios or C_{end} to trigger intensified monitoring, dose adjustment, or alternative routes of administration. Compared with linezolid, an alternative agent, which has been shown to achieve relatively better CSF/plasma ratios of 30–70%, the therapeutic challenge is particularly pronounced as vancomycin remains the mainstay agent for Gram-positive CNS infections but demonstrates intrinsically poor and unpredictable CNS penetration, underscoring an unmet need for improved therapeutic strategies in this setting.[24]

Study Limitations

Several limitations of this study should be acknowledged. First, the small sample size (n = 9) substantially limited the statistical power of the popPK model and may have contributed to the inability to identify significant covariates influencing vancomycin PK. As a result, the regression analyses and popPK modeling should be interpreted cautiously and regarded as exploratory and hypothesis-generating rather than confirmatory. The limited sample size also increases the risk of model overfitting and restricts the generalizability of the findings. Meaningful pharmacodynamic assessment was not feasible, as only two patients had microbiologically confirmed infections, precluding evaluation of the relationship between CSF exposure and pathogen MIC.

Moreover, the diagnosis of ventriculitis included both confirmed and suspected cases, and some criteria, such as CSF turbidity and routine biochemical parameters, may be considered subjective. This uncertainty reflects real-world clinical practice, where early differentiation between infectious ventriculitis and sterile inflammation following IVH remains challenging in patients with EVDs. Previous studies have shown that conventional CSF markers alone may be insufficient for reliable diagnosis, and alternative parameters such as the cell index have been proposed.[11] This diagnostic heterogeneity may have contributed to variability in observed CSF penetration.

Furthermore, CSF sampling was restricted to procedures performed by physicians, which limited the number of eligible patients. This constraint may have introduced selection bias, as only patients requiring clinically indicated CSF sampling were included. Finally, this study was not conducted under a pre-registered protocol, which may limit

transparency regarding analytic decisions and should be considered when interpreting the results. Future studies with larger sample sizes, standardized sampling strategies, and prospective preregistration are warranted to validate these findings and better characterize vancomycin penetration dynamics in patients with ICH and EVDs.

Conclusion

To our knowledge, this is the first study to report real-world data of vancomycin CSF penetration in neurosurgical population in Taiwan. Our study provides new insights into the CSF penetration of vancomycin in patients with ICH and EVDs, demonstrating lower and variable $AUC_{CSF/plasma}$ ratios compared to previously reported values. C_{end} appeared to correlate well with overall CSF exposure relative to plasma and may serve as a practical surrogate marker when direct CSF monitoring is not feasible. From a clinical perspective, these results indicate that standard intravenous vancomycin dosing may not reliably achieve therapeutic CSF concentrations in this high-risk population, highlighting the need for intensified TDM, individualized dosing strategies, and consideration of alternative routes of administration, such as intraventricular therapy, in selected patients. Importantly, this study provides a PK foundation for future therapeutic optimization in CNS infections. The observed variability in CSF penetration supports the development of MIPD approaches, and justifies prospective, multicenter studies to validate surrogate markers, refine popPK models, and evaluate whether individualized dosing strategies can improve clinical outcome in patients with VAI.

Data Sharing Statement

Datasets generated and/or analyzed during the current study are available from Shu-Wen Lin, the corresponding author, on reasonable request.

Ethics Approval

This study was conducted in accordance with the Declaration of Helsinki, and ethical approved was obtained from the National Taiwan University Hospital Research Ethics Committee (202302126RINA).

Consent to Participate

All patients, or their legally authorized representatives when applicable, provided written informed consent prior to participation in this study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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