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Comparative effectiveness of monotherapy vs. combination therapy for postoperative central nervous system infections in neurosurgical patients: a retrospective cohort study

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Abstract

Background Although clinical guidelines recommend vancomycin-based combination therapy for patients with postoperative intracranial infections in neurosurgery, the trend of global bacterial resistance and the management of antimicrobial agents have made monotherapy a common treatment option for some patients. This study aims to compare the efficacy of single-drug therapy (SDT) versus vancomycin combination therapy (VCT) in treating central nervous system infections (CNSIs) following neurosurgery.

Methods A retrospective cohort study was conducted, adjusting for various covariates such as length of stay (LoS), admission status, age, comorbidity status (Charlson Comorbidity Index, CCI), surgical and incision levels, and duration of surgery (DOS) using propensity score matching (PSM) with a 1:2 ratio. The treatment effects of the two empirical treatment regimens were evaluated through PSM and logistic regression for dual robustness.

Results A total of 539 patients met the inclusion criteria, with 177 cases in SDT and 101 cases in VCT after PSM. The clinical cure rate was 76% in the SDT compared to 90% in the VCT ($p=0.007$) after PSM. Of the result of antibiotic susceptibility testing, only 13.9% of cases identified specific pathogens, of which gram-positive cocci were the dominant. VCT was significantly more effective than SDT, both in unadjusted (OR 2.941, 95% CI 1.434–6.607, $p=0.005$) and adjusted models (OR 3.605, 95% CI 1.611–8.812, $p=0.003$). Gender, race, and surgical complexity were significant factors influencing treatment choice; female patients and those with complex surgeries were less likely to receive SDT. Although SDT was practically effective for treating CNSIs, VCT proved superior for complex infections.

Conclusion The findings of this study suggest that, given concerns about antibiotic resistance and the varying complexities of infections, while SDT is effective in certain cases, VCT remains the preferred choice for complex CNSIs. This research provides important references for clinical practice, highlighting the need to consider multiple factors when selecting treatment options and advancing the understanding of treatment strategies for postoperative central nervous system infections.

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Introduction

Postoperative central nervous system infections (CNSIs) have emerged as critical complications, especially following cranial surgeries in modern neurosurgery [1]. These infections present significant challenges due to their high pathogenicity and difficulty in treatment, adversely impacting both patient health and healthcare systems [2]. The occurrence of CNSIs lowers patient survival rates and quality of life and places a considerable strain on healthcare teams and resources [3]. In recent years, the rising number of neurosurgical procedures and an increasing elderly patient population have led to a higher incidence of CNSIs, further complicating clinical management [4].

The *Chinese Expert Consensus on the Diagnosis and Treatment of Central Nervous System Infections in Neurosurgery 2021* reported that the incidence of postoperative CNSIs ranges from 4.6 to 25%, accounting for 0.8–7% of all CNSI cases [5]. The primary causes of postoperative CNSIs include microtrauma from surgical procedures and the subsequent immunosuppressive state, creating an entry pathway for pathogens into the central nervous system [6]. If timely and effective infection control measures are not implemented during the postoperative recovery phase, CNSIs can lead to severe neurological damage, systemic infections, and even death [7]. CNSIs often manifest as meningitis, brain abscesses, or ventriculitis, and their complexity makes treatment particularly challenging [1, 6].

Antibiotic resistance has become a significant concern in the treatment of CNSIs, particularly in neurosurgical patients. The spread of resistant bacteria and the emergence of new multidrug-resistant strains, such as MRSA and VRE, have diminished the effectiveness of traditional antibiotic regimens, resulting in prolonged disease courses and higher recurrence risks [8, 9]. Consequently, vancomycin-based combination therapy is increasingly adopted in clinical practice to enhance treatment outcomes and mitigate the risk of bacterial resistance [10, 11].

Differences between international and Chinese guidelines and regulations regarding the rational use of antibacterial agents for antibiotic selection add to the complexity of CNSI management in neurosurgery. Chinese guidelines and regulations prioritise the rational use of antibiotics and impose strict restrictions on certain drugs to control the spread of resistance [12]. While this approach has effectively curbed the spread of resistant bacteria, it has also limited treatment options, particularly for resistant strains. In contrast, U.S. and European guidelines offer more flexibility, advocating personalised combination therapy tailored to pathogen types and infection characteristics [11, 13].

Laboratory testing plays a crucial role in confirming infectious pathogens, yet the diagnostic positivity rate for postoperative infections in neurosurgery remains low, complicating precise diagnosis and individualised treatment [14]. This challenge is especially pronounced in the context of multidrug-resistant strains, where the accuracy of diagnostic results directly affects treatment decisions [15]. The atypical presentation of infections and the diversity of resistant pathogens further increase treatment uncertainty.

Given these challenges, this study conducted a retrospective cohort analysis to compare the effectiveness of monotherapy versus combination therapy in empirically treating CNSIs in neurosurgical patients. The findings aimed to provide further scientific evidence to optimise antimicrobial therapy in neurosurgery, supporting clinicians in managing resistant strains, optimizing treatment strategies, and improving infection control outcomes while offering new insights into future CNSI treatment approaches.

Method

Study design and ethical considerations

This cohort study aligned with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Appendix 1) [16]. The study protocol was approved by the State Key Laboratory of Pathogenesis, Prevention, and Treatment of High Incidence Diseases in Central Asia (Grant No: SKL-HIDCA-2023-YX7). Ethical approval was obtained from the First Affiliated Hospital Ethics Committee of Xinjiang Medical University (Approval No: K202401-07). In accordance with national regulations "*The Ethical Review of Biomedical Research Involving Humans (2016)*" from the Chinese National Health and Family Planning Commission [17], the need for informed consent was waived as this study used retrospective, anonymized patient data. The aforementioned Ethics Committee granted the waiver.

Study population

This study included patients who underwent neurosurgical procedures at the First Affiliated Hospital of Xinjiang Medical University between January 1, 2019, and December 31, 2023. From this population, a cohort of patients with confirmed postoperative infections was identified. The effectiveness of various empirical initial antibacterial

therapy regimens was then assessed based on patient outcomes in this cohort.

Data collection

Patient data were retrospectively extracted from the hospital's electronic medical records (EMR) system and were classified into demographic, social, and clinical categories. Demographic and social information included variables such as gender and age, while clinical data encompassed diagnosis and treatment specifics. Clinical data variables included primary diagnosis, admission status (categorized as standard, critical, or emergent), preoperative hospital length of stay (LoS), total Los, duration of surgery (DOS), and surgical information. Notably, given the critical importance of the timing of antibacterial agent administration and the absence of reported antibiotic susceptibility testing (AST) results when the initial empirical agent was given to the patient, data on cerebrospinal fluid (CSF) bacterial culture and AST were collected to assess the appropriateness of the empirical initial treatment strategy.

Details of antibacterial therapy were collected, including agent types, dosages, administration frequencies, and timing of the treatment course. Surgical information encompassed surgeons' identity to reflect their experience and surgical and incision levels, indicating the complexity of surgical interventions and the associated infection risk at the site. Diagnoses were coded according to the International Classification of Diseases, 10th Revision (ICD-10). Surgical procedures were documented following the Surgical Operation Classification Code (SOCC) National Clinical Version 3.0, established by the National Health Commission (NHC) of the People's Republic of China (detailed SOCC provided in Supplementary file Appendix 2).

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) patients with a confirmed diagnosis of post-neurosurgical central nervous system infection (NCNSI), meeting the diagnostic criteria established by expert consensus on NCNSIs, and (2) patients aged ≥ 18 years. Exclusion criteria were: (1) re-admission within 30 days; (2) presence of brain abscesses; (3) severe hepatic or renal dysfunction; (4) recent interventional surgery; (5) women who were pregnant or in the peripartum period; (6) patients who only received antibacterial prophylaxis or who did not receive antibacterial therapy; and (7) patients with confirmed infections at other body sites, such as pulmonary infections.

Outcome measures

The primary outcome of this study was the effectiveness of initial empirical antibacterial treatment, classified as effective or ineffective. Effectiveness was defined as a critical improvement in the patient's infection symptoms, leading to the discontinuation of medication due to the resolution of the infection. Ineffectiveness was determined by the absence of symptom improvement, or worsening during initial empirical treatment, or by the need to switch to an alternative antibacterial agent after a standard treatment assessment duration (typically three days). Death during the treatment period was categorised as an ineffective outcome.

Treatment exposure

This cohort study defined and categorised treatment exposures based on initial empirical treatment regimens extracted from patients' EMR. Treatment regimens were classified into single-drug therapy (SDT) and vancomycin-based combination therapy (VCT). SDT was defined as the administration of a single antibacterial agent in patients with CNSIs. In contrast, VCT involved the concurrent use of vancomycin with additional antibacterial agents. This classification facilitated a comparative analysis of these two therapeutic approaches in managing CNSIs within a neurosurgical context. The antimicrobial agents selected for treating hospital-acquired CNSIs adhered to established guidelines, with recommended dosages including vancomycin 1 g q12h, meropenem 2 g q8h, ceftazidime 2 g q8h, and ceftriaxone 2 g q12h. This approach allowed for a standardised comparison of therapeutic effectiveness between SDT and VCT in the study cohort. As this is a retrospective cohort study, the treatment regimens were determined by surgeon's clinical judgment based on the patient's clinical condition, infection severity, and institutional guidelines at the time of treatment.

Covariates

In this cohort study, we identified and documented baseline patient characteristics that could potentially influence the selection of antibacterial therapy. These covariates included preoperative LoS, admission status, age, comorbidity status, surgical and incision levels, and DOS. To quantify comorbidities, the Charlson Comorbidity Index (CCI) using validated algorithms was used to measure the comorbidities status, which utilised 19 comorbid conditions identified through ICD-10 codes in the EMR (Detailed algorithm provided in Supplementary file Appendix 3) [18]. Collecting these covariates ensured the precise classification of treatment regimens and enabled a comprehensive evaluation of their effectiveness. This approach allowed for a robust assessment of how baseline characteristics impacted treatment outcomes within the study population.

Statistical analysis

Descriptive statistical methods were used to summarise patient characteristics, exposure and outcome variables, and covariates. Differences in categorical and continuous variables were assessed for statistical significance using the Chi-square test and Wilcoxon signed-rank test, respectively, with a significance level set at $P < 0.05$.

Machine learning approach: random forest model

To identify potential predictors of the binary outcome variable, a Random Forest classifier was employed. The dataset was split into training (80%) and testing (20%) sets. The model was configured with the following hyperparameters: 100 decision trees, a minimum sample split of 2, a minimum leaf node sample size of 1, and Gini impurity as the splitting criterion. The maximum depth of the trees was left unrestricted, and the maximum number of features considered for splitting at each node was set to "auto." Bootstrap sampling was applied during training, meaning each tree was trained on a random subset of the data with replacement. Out-of-bag (OOB) error estimation was used to provide an unbiased assessment of model performance. The Random Forest model was used to identify potentially valuable factors, which were subsequently evaluated further using multilevel logistic regression.

Addressing confounding: propensity score matching (PSM)

Given the retrospective cohort design of this study, patients were not randomly assigned to the SDT or VCT groups. To mitigate potential confounding, propensity score matching (PSM) was employed to estimate the likelihood of assignment to either group, incorporating relevant baseline covariates. A 1:2 matching ratio was applied using a calliper of 0.2, consistent with recommendations from prior research suggesting that the logit of the propensity score should be matched using callipers set at 0.2 of the standard deviation of the logit of the propensity score [19].

Multilevel logistic regression

Multilevel logistic regression analyses were performed to evaluate the association between SDT and VCT before and after propensity score matching. This approach further addressed confounding between exposure and covariates within the model. The propensity score was calculated using covariates such as age, gender, length of surgical procedure, admission status, CCI, surgical levels, and incision levels. This doubly robust approach helped reduce indication bias and enhance the reliability of the estimates [20]. All analyses were conducted using the statistical software R v.3.6.3 (R Core Team, 2021), implemented in Studio v.1.2.5042 (R Studio Team, 2020).

Results

In our study, there were 539 patients with confirmed post-surgical infection diagnoses through 12,519 patients undergoing surgical interventions, and the incidence rate of post-surgical infection was 6.86%. A flow diagram illustrating the cohort identification is presented in Fig. 1. Of the 539 patients with confirmed post-surgical infection, 430 (79.8%) received SDT, while 109 (20.2%) received VCT. After PSM, there were 177 cases in the SDT group and 101 cases in the VCT group.

Before PSM, there was a significant difference in effectiveness between the two treatment strategies ($p = 0.002^*$), with 76.58% of patients in the single-drug therapy group responding effectively compared to 23.19% in the combination therapy group. After adjustment by PSM, the effectiveness rates between the two treatment groups remained significantly different ($p = 0.007$), with 76.27% of patients in the single-drug therapy group and 90.10% in the combination therapy group showing effectiveness. In terms of gender distribution, a significant difference was observed before matching ($p = 0.002$), with a higher proportion of males in the combination therapy group compared to the single-drug therapy group. However, after PSM, no significant gender differences were noted ($p = 0.485$). Age did not differ significantly between the two groups, both before and after PSM ($p = 0.826$ and $p = 0.921$, respectively). Ethnicity showed a trend toward significance before matching ($p = 0.058$) but no significant differences after matching ($p = 0.938$). The LoS and admission route also showed no significant differences between the groups, both before and after matching. Regarding the CCI, most patients in both treatment groups had 0 CCI points, with no significant differences in comorbidity distribution before or after PSM. Surgical characteristics, including surgery duration and level of surgery, did not differ significantly between the groups. (Table 1)

Among the 539 patients in the study, benign and malignant tumours (C and D codes) were the most prevalent conditions, accounting for 60.2% of the cases ($n = 325$), followed by cerebrovascular diseases (I code), representing 18.7% of the cases ($n = 101$). The third was the nervous system diseases (G code), constituting 13.2% ($n = 71$). The most common condition was benign neoplasm of the pituitary gland (D35.2), with 64 cases. Other frequently reported conditions included benign neoplasm of the cerebral meninges (D32.0) with 54 cases, and benign neoplasm of the brain unspecified (D33.3) with 35 cases. Notably, malignant neoplasms of different brain regions were also significant, including unspecified malignant neoplasm of the brain (C71.9) and malignant neoplasm of the temporal lobe (C71.2), each with 15 cases. Additionally, there were 16 cases of subarachnoid haemorrhage from the middle cerebral artery (I60.2) and nontraumatic

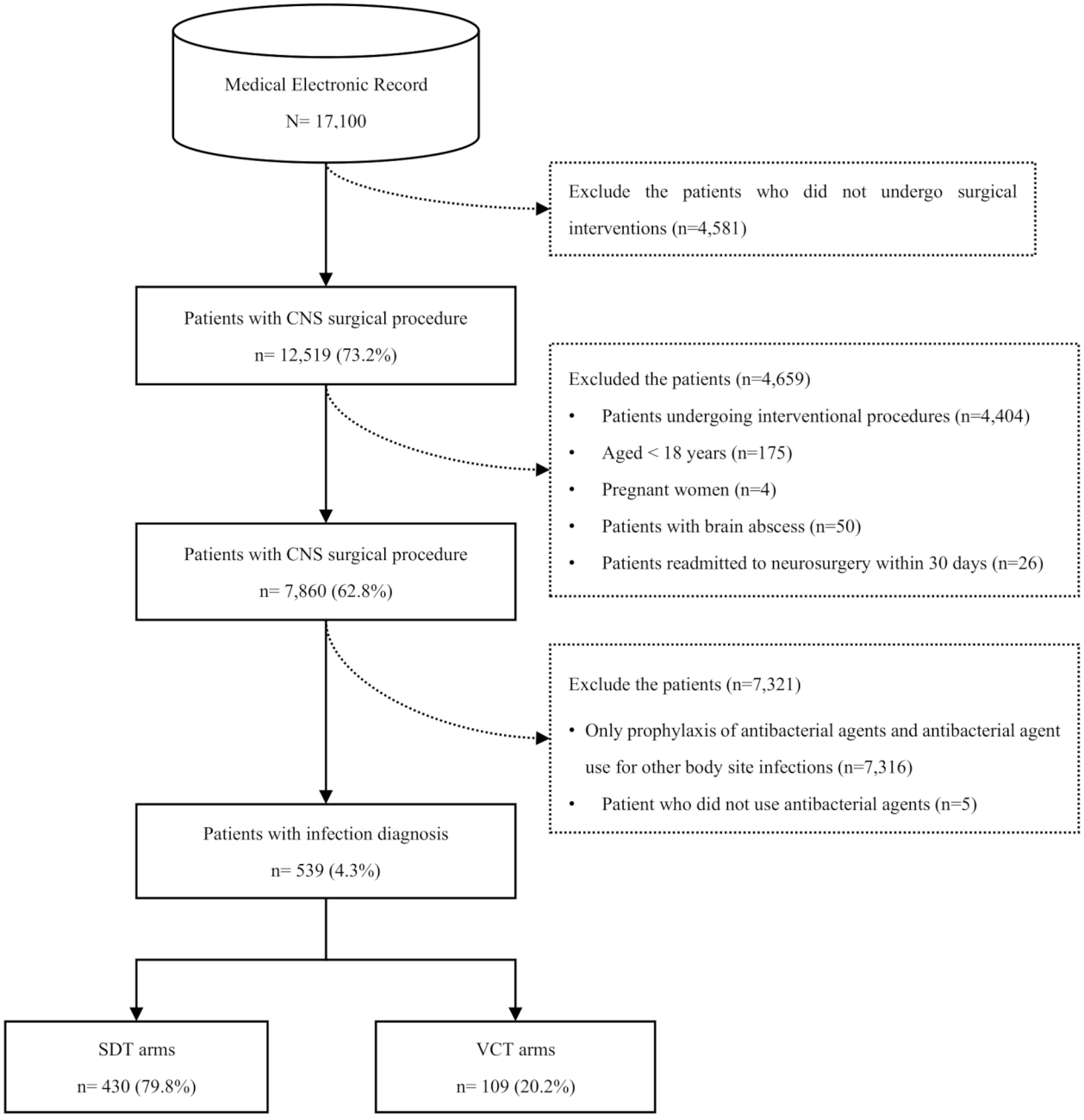

Fig. 1 The inclusion process of patients with confirmed diagnoses by two antibacterial therapies
Note: CNS: the central nervous system; SDT: singe-drug therapy; VCT: vancomycin-based combination therapy

intracerebral haemorrhage in the hemisphere, subcortical (I61.0). Less common conditions included trigeminal neuralgia (G50.0) with 10 cases and various forms of epilepsy and recurrent seizures (G40.8, G40.2). Rare conditions, with only one case each, included Parkinson's disease (G20.x), malignant neoplasm of the cerebellum (C71.6), and other disorders such as cerebrospinal fluid leak (G96.0) and echinococcosis of the brain (B67.6). (Detailed diagnostic codes are provided in Supplementary file Appendix 4.)

Out of the 539 patients who received antimicrobial treatment, cerebrospinal fluid (CSF) examinations were performed on 432 patients (80.15%) either before or within one day after the start of antibacterial therapy. Among these, 401 patients (92.82%) exhibited abnormal total white blood cell counts, 422 patients (97.69%) had abnormal Pandy test results, 273 patients (63.19%) showed abnormal chloride levels, and 252 patients (58.33%) demonstrated abnormal glucose levels.

Table 1 Baseline characteristics for treatment effectiveness before and after propensity score matching

Variable	Unadjusted values			Adjusted values by PSM		
	Single-drug therapy *n* = 427	Combination therapy *n* = 109	*p* Value	Single-drug therapy *n* = 177	Combination therapy *n* = 101	*p* Value
Effectiveness (%)			0.002*			0.007*
Effective	327 (76.58)	99 (23.19)		135 (76.27)	91 (90.10)	
Ineffective	100 (23.42)	10 (8.93)		42 (23.73)	10 (9.90)	
Gender (%)			0.002*			0.485
Male	226 (52.90)	76 (69.72)		114 (64.4)	70 (69.3)	
Female	201 (47.10)	33 (30.38)		63(35.6)	31(30.7)	
Age/Years [mean (SD)]	49.88 (12.90)	50.19 (13.79)	0.826	50,01 (13.12)	50.18 (13.99)	0.921
Ethnicity (%)			0.058			0.938
Han	189 (44.30)	56 (51.37)		89 (50.30)	55 (54.50)	
Uyghur	140 (32.80)	32 (29.35)		58 (32.8)	30 (29.7)	
Kazakh	52 (12.20)	6 (5.50)		14 (7.9)	6 (5.9)	
Hui	33 (7.70)	7 (6.42)		8 (4.5)	5 (5.0)	
Other#	13 (3.00)	8 (7.34)		8 (4.5)	5 (5.0)	
Length of Hospital Stay/Days[Median (IQR)]	29 (22.00–40.00)	31 (22.00–42.00)	0.565	30 (21.00–41.00)	31 (22.00–43.00)	0.585
Admission Route (%)			0.638			0.825
Emergency	1221(28.3)	33 (30.27)		49 (27.7)	30 (29.7)	
Outpatient	303 (71.00)	76 (69.63)		128 (72.3)	71 (70.3)	
Other	3 (0.7)	0 (0.00)		0 (0.00)	0 (0.00)	
CCI (%)			0.083			0.957
0 points	358 (83.80)	91 (83.48)		151 (85.3)	85 (84.2)	
1 points	56 (13.10)	4 (3.67)		20 (11.3)	12 (11.9)	
2 points	13 (3.00)	12 (11.01)		6 (3.4)	4 (4.0)	
3 points	0 (0.00)	1 (0.92)		0 (0.00)	0 (0.00)	
6 points	0 (0.00)	1 (0.92)		0 (0.00)	0 (0.00)	
Duration of Surgery/Minutes [Median (IQR)]	270 (190.00-340.00)	280 (220.00-335.00)	0.400	280 (220.00-350.00)	280 (220.00-335.00)	0.954
Surgical Level (%)			0.215			0.776
Level 2	37 (8.70)	4 (3.67)		8 (4.5)	3 (3.0)	
Level 3	51 (11.90)	14 (12.84)		23 (13.0)	12 (11.9)	
Level 4	339 (79.40)	91 (83.49)		146 (82.5)	86 (85.1)	
Surgical Incision Level (%)			0.123			0.965
Level 1	345 (80.30)	92 (84.40)		154 (87.0)	87 (86.1)	
Level 2	13 (3.00)	1 (0.92)		2 (1.1)	1 (1.0)	
Level 3	6 (1.40)	0 (0.00)		0 (0.00)	0 (0.00)	
Level 4	65 (15.20)	15 (13.76)		21 (11.9)	13 (12.9)	
Level 5	0 (0.00)	1 (0.92)		0 (0.00)	0 (0.00)	

Note: SD: standard deviation; IQR: interquartile range; CCI: Charlson Comorbidity Index; Other#: Tibetan, Manchu, Dongxiang, Kirgiz, Mongolian, Uzbek, Xibe

Out of the 539 patients, 446 (82.7%) underwent CFS bacterial culture and antibiotic susceptibility testing (AST), with each case tested at least twice. Among these 446 cases, only 62 (13.9%) yielded positive results for CFS bacterial culture on at least one occasion, while the remaining 384 cases (86.1%) showed no specific bacterial pathogens identified. In our study, we identified a variety of pathogens from cerebrospinal fluid (CSF) samples. The most frequently identified pathogen was *Staphylococcus epidermidis*, present in 14 cases, all of which showed a 100% match with the identified multidrug-resistant pathogen (MRP). Other significant pathogens included *Acinetobacter baumannii* and *Staphylococcus hominis*, with 9 and 4 cases respectively, both demonstrating a 100% MRP match. *Staphylococcus aureus* and *Klebsiella pneumoniae* were also notable, each identified in 3 cases with a 100% MRP match. Additionally, *Corynebacterium striatum* presented a unique case where only 50% of the identified cases matched the MRP. Among other pathogens such as *Micrococcus luteus*, *Enterococcus faecium*, *Streptococcus pneumoniae*, and *Pseudomonas aeruginosa*, all cases showed a 100% MRP match. Interestingly, *Acinetobacter lwoffii* was the only pathogen identified from CSF that did not show any MRP match. Overall,

Table 2 The pathogens identified from CSF

Identified the pathogens from CSF	No of Cases	Number of MRP
Staphylococcus epidermidis	14	14 (100%)
Klebsiella pneumoniae	3	3 (100%)
Corynebacterium striatum	2	1 (50%)
Acinetobacter baumannii	9	9 (100%)
Micrococcus luteus	2	2 (100%)
Staphylococcus haemolyticus	3	3 (100%)
Corynebacterium strasburgense	1	1 (100%)
Enterococcus gallinarum (Group D)	1	1 (100%)
Enterococcus faecium (Group D)	2	2 (100%)
Staphylococcus hominis	4	4 (100%)
Streptococcus parasanguinis	1	1 (100%)
Acinetobacter lwoffii	1	0 (0%)
Enterobacter cloacae	1	1 (100%)
Haemophilus ducreyi	1	1 (100%)
Brevundimonas diminuta	1	1 (100%)
Staphylococcus aureus	3	3 (100%)
Citrobacter freundii	1	1 (100%)
Enterococcus casseliflavus (Group D)	1	1 (100%)
Streptococcus pneumoniae	2	2 (100%)
Pseudomonas oryzihabitans	1	1 (100%)
Streptococcus mitis	1	1 (100%)
Bacillus cereus	1	1 (100%)
Pseudomonas aeruginosa	2	2 (100%)
Staphylococcus warneri	1	1 (100%)
Enterococcus faecalis (Group D)	1	1 (100%)
Escherichia coli	1	1 (100%)
Pseudomonas mendocina	1	1 (100%)

MRP: multidrug-resistant pathogen

the identification and MRP matching of pathogens from CSF samples provided crucial insights into the microbial landscape associated with these cases (Table 2).

To identify potentially valuable factors by Random Forest, the data preprocessing involved handling missing values, which accounted for 29.13% of the dataset, leaving 70.87% valid entries. The final dataset consisted of 539 entries, and feature importance was assessed based on the model's output. On the training set, the model demonstrated perfect classification performance, achieving an accuracy of 1.0, along with balanced precision, recall, and F1-scores of 1.0 for both outcome classes. This indicates that the model learned the underlying patterns in the training data exceptionally well, with no errors during the training phase. However, performance on the test set revealed a slight decline in accuracy. The overall test accuracy was 0.82, with the negative class (0) achieving a precision of 0.83, a recall of 0.98, and an F1-score of 0.90. For the positive class (1), precision and recall were both 0, reflecting the very low number of positive cases in the test set. The model's average F1-score across both classes was 0.75, with an overall average recall of 0.49 and average precision of 0.41.

Table 3 Variable weights assessed by random forest

Feature	Weight Value
Gender	0.016
Age	0.095
Ethnicity	0.038
Admission Route	0.008
Admission Condition	0.011
Condition at Admission	0.028
Readmission	0.017
Length of Stay	0.161
Pre-operative LoS	0.103
Surgical Level	0.016
Incision Level	0.015
Single Dose	0.017
Combined Medication	0.032
Total White Blood Cell Count in CFS	0.102
Protein Quantification in CFS	0.09
Chlorine in CFS	0.101
Glucose in CFS	0.093

The Random Forest classifier identified hospitalization-related features as the most influential predictors, with LoS (0.161), preoperative LoS (0.103), and surgical level (0.016) having the highest impact on the model's predictions. Other significant features included age (0.095), white blood cell count (0.102), and protein quantification (0.090). In contrast, demographic variables such as gender (0.016), ethnicity (0.038), and admission type (0.008) contributed relatively little to the model's decision-making process. (Table 3)

Table 4 summarizes the logistic regression analysis examining factors influencing the selection of treatment strategy, with both univariate and multivariate results presented. In the univariate analysis, gender was significantly associated with treatment choice. Specifically, females were less likely to receive combination therapy compared to males (OR: 0.490, 95% CI: 0.309–0.763; $p = 0.002$). This association remained highly significant in the multivariate model, with females being 2.42 times more likely to be assigned to combination therapy (OR: 2.417, 95% CI: 1.445–4.126; $p < 0.001$). Ethnicity also had a notable impact on treatment selection. In the univariate analysis, Kazakh patients were significantly less likely to receive combination therapy (OR: 0.386, 95% CI: 0.142–0.881; $p = 0.037$). This association persisted in the multivariate model (OR: 0.381, 95% CI: 0.132–0.942; $p = 0.050$), suggesting a reduced likelihood of combination therapy for Kazakh patients. Additionally, the Hui ethnic group showed a trend toward a lower likelihood of receiving combination therapy, although this did not reach statistical significance in the multivariate analysis (OR: 0.356, 95% CI: 0.106–0.986; $p = 0.065$). Surgical complexity also played a role in treatment selection. In the multivariate model, patients undergoing level 4

Table 4 Logistic regression for factors influencing the selection of treatment strategy

Variable	Univariate Regression		Multivariate Regression	
	OR (95%CI)	*p* Value	OR (95%CI)	*p* Value
Gender (%)				
Male (Reference)	-	-	-	-
Female	0.490 (0.309–0.763)	0.002*	2.417(1.445–4.126)	< 0.001*
Age/Years [mean (SD)]	1.002 (0.986–1.018)	0.795	1.005(0.986–1.024)	0.610
Ethnicity (%)				
Han (Reference)	-	-		
Uyghur	0.779(0.475–1.261)	0.315	0.594(0.333–1.045)	0.074
Kazakh	0.386(0.142–0.881)	0.037*	0.381(0.132–0.942)	0.050
Hui	0.723(0.281–1.637)	0.465	0.356(0.106–0.986)	0.065
Other#	2.098(0.795–5.240)	0.118	2.824(0.917–8.587)	0.065
Length of Stay/Days[Median (IQR)]	1.002 (0.999–1.012)	0.731	1.005(0.992–1.017)	0.379
Admission Route (%)				
Emergency (Reference)	-	-	-	-
Outpatient	0.923 (0.581–1.464)	0.706	0.872(0.476–1.567)	0.653
Other	0.518 (0.000-Inf)	0.645	< 0.001 (0.000-Inf)	0.993
CCI (%)				
0 points (Reference)	-	-	-	-
1 points	1.176 (0.624–2.385)	0.632	0.714(0.320–1.489)	0.387
2 points	0.819 (0.282–2.962)	0.733	1.109(0.281–3.667)	0.871
3 points	-	-	-	-
6 points	-	-	-	-
Duration of Surgery/Minutes [Median (IQR)]	1.001 (0.999–1.002)	0.388	1.001(0.998–1.002)	0.940
Surgical Level (%)				
Level 2 (Reference)	-	-	-	-
Level 3	2.607 (0.856–9.767)	0.114	4.287(1.004–24.128)	0.065
Level 4	2.535 (0.986–8.619)	0.084	5.415(1.483–27.793)	0.020*
Surgical Incision Level (%)				
Level 1 (Reference)	-	-	-	-
Level 2	0.288 (1.018–4.383)	0.234	0.404(0.021–2.393)	0.408
Level 3	-	-	-	-
Level 4	0.940 (1.580–4.709)	0.640	2.609(0.993–7.144)	0.054
Level 5	-	-	-	-

Other#: Tibetan, Manchu, Dongxiang, Kirgiz, Mongolian, Uzbek, Xibe

surgeries had a significantly higher likelihood of receiving combination therapy (OR: 5.415, 95% CI: 1.483–27.793; $p = 0.020$), indicating that more complex surgeries were associated with this treatment strategy. A similar trend was observed for level 3 surgeries (OR: 4.287, 95% CI: 1.004–24.128; $p = 0.065$), although this did not reach statistical significance.

Table 5 presents the logistic regression analysis for factors associated with treatment effects, both unadjusted and adjusted by propensity score matching (PSM). In the unadjusted analysis, combination therapy was significantly associated with better treatment outcomes compared to single-drug therapy (OR: 2.941, 95% CI: 1.434–6.607; $p = 0.005$). After adjustment by PSM, this association remained significant, with an odds ratio of 3.605 (95% CI: 1.611–8.812; $p = 0.003$), indicating that patients receiving combination therapy had a significantly higher likelihood of achieving better treatment effects. In terms of other factors, length of stay (LoS) was a consistent predictor of treatment outcomes. In both unadjusted and adjusted models, a shorter length of stay was associated with improved treatment effects (unadjusted OR: 0.965, 95% CI: 0.951–0.978; $p < 0.001$; adjusted OR: 0.956, 95% CI: 0.933–0.978; $p < 0.001$), highlighting the importance of timely interventions. Admission route also influenced treatment outcomes. Patients admitted through outpatient routes were less likely to experience favorable treatment effects compared to those admitted via emergency routes. In the unadjusted model, outpatient admissions had an OR of 0.502 (95% CI: 0.275–0.918; $p = 0.025$), which was further reduced to 0.309 (95% CI: 0.121–0.763; $p = 0.011$) after adjusting for other factors. This suggests that outpatient admissions were associated with worse treatment outcomes. Ethnicity and surgical characteristics did not demonstrate significant associations with treatment effects. While the

Table 5 Logistic regression of the factors associated with treatment effects

Factors	Unadjusted values		Adjusted values by PSM	
	OR (95%CI)	*p* Value	OR (95%CI)	*p* Value
Treatment Plan (Single-drug therapy)				
Combination therapy	2.941 (1.434–6.607)	0.005*	3.605 (1.611–8.812)	0.003*
Gender (Female)				
Male	1.239 (0.749–2.054)	0.402	0.878 (0.385–1.940)	0.751
Age	1.003 (0.984–1.023)	0.753	0.990 (0.960–1.021)	0.530
Ethnicity (Han)				
Uyghur	0.992 (0.551–1.795)	0.977	0.952 (0.406–2.259)	0.909
Kazakh	0.793(0.380–1.711)	0.545	0.941 (0.271–3.876)	0.927
Hui	1.395 (0.557–3.864)	0.494	1,845,845 (0.000-Inf)	0.956
Other#	1.582 (0.432–8.068)	0.527	2.058 (0.300-41.768)	0.529
LoS	0.965 (0.951–0.978)	< 0.001*	0.956 (0.933-0,978)	< 0.001*
Admission Route (Emergency)				
Outpatient	0.502 (0.275–0.918)	0.025*	0.309 (0.121–0.763)	0.011*
Other	-	-	-	-
CCI (0 points)				
1 points	0.813 (0.403–1.716)	0.574	0.573 (0.182–1.897)	0.345
2 points	0.487 (0.161–1.576)	0.210	1.275 (0.231–10.425)	0.795
3 points	-	-	-	-
6 points	-	-	-	-
Duration of Surgery	1.000 (0.998–1.003)	0.785	0.999 (0.996–1.007)	0.619
Surgical Level (Level 2)				
Level 3	3.831 (1.035–15.098)	0.047*	3.131 (0.115–48.833)	0.422
Level 4	1.554 (0.529–4.420)	0.412	0.925 (0.041–8.394)	0.950
Surgical Incision Level (Level 1)				
Level 2	0.826 (0.205–4.277)	0.800	-	-
Level 3	-	-	-	-
Level 4	1.795 (0.711–4.763)	0.225	0.978 (0.162–8.020)	0.982
Level 5	-	-	-	-

Note: SD: standard deviation; IQR: interquartile range; LoS: Length of Stay; CCI: Charlson Comorbidity Index; SDT: Single-drug therapy; VCT: vancomycin-based combination therapy; Other#: Tibetan, Manchu, Dongxiang, Kirgiz, Mongolian, Uzbek, Xibe

unadjusted model showed some variation, such as the association between surgical level 3 and better outcomes (OR: 3.831, 95% CI: 1.035–15.098; $p = 0.047$), this effect did not persist after adjustment (adjusted OR: 3.131, 95% CI: 0.115–48.833; $p = 0.422$). Other variables, including age, comorbidity (CCI), surgical duration, and surgical incision level, did not significantly affect treatment outcomes in either the unadjusted or adjusted models. In summary, combination therapy, shorter length of stay, and emergency admission were significant factors associated with better treatment outcomes. These findings emphasize the importance of timely and appropriate treatment strategies, particularly combination therapy, in improving patient outcomes. Other demographic and clinical factors, including ethnicity, surgery complexity, and comorbidities, did not show consistent associations after adjusting for potential confounders.

Discussion

This study aimed to compare the effectiveness of SDT and combination therapy in the empirical treatment of central nervous system infections (CNSIs) in neurosurgical patients. Our findings indicate that SDT, while effective for certain cases, may not be the optimal treatment for all types of CNSIs, particularly in complex infections where VCT was shown to have superior outcomes. In addition, we found that the incidence of postoperative CNSIs in neurosurgical patients was 6.86%. This result reflects the level of infection control at this medical institution and provides important epidemiological data on CNSIs in western China.

Previous studies have demonstrated that age, gender, ethnicity, and duration of surgery are significant risk factors for postoperative CNSIs, affecting treatment outcomes and potentially influencing clinicians' choices of drug therapy [21]. Therefore, this study included these variables in the multilevel logistic regression analysis. On the other hand, all cases that received VCT in our study experienced an intensive care unit (ICU) stay. The results

indicate that surgical duration and ICU admission status are significant factors associated with the choice between SDT and VCT. This finding is consistent with previous research, likely due to the complexity of major surgeries, longer surgical times, and larger surgical incision exposure areas, which increase the risk and severity of infections [22, 23].

Despite the guidelines recommending vancomycin-based combination therapy for intracranial infections, including third or fourth-generation cephalosporins and anti-pseudomonal β-lactam antibiotics that can cross the blood-brain barrier [11], our study only included ceftazidime, ceftriaxone, meropenem, and vancomycin. This limitation is due to the standard inventory constraints in tertiary hospitals in China, including our hospital, which regularly stocks only these four antibiotics for treating intracranial infections [24]. If a patient's symptoms are not well controlled, other suggested antibiotics can be temporarily procured. However, a review of the neurosurgery department's antibiotic procurement records from 2019 to 2023 revealed no additional antibiotics were purchased due to inadequate treatment outcomes. This indicated these four antibiotics provided effective treatment. Furthermore, cerebrospinal fluid (CSF) cultures were performed on less than half of the patients within one day before or after starting antimicrobial therapy, with a positive culture rate of less than 15%. Therefore, CSF culture results have limited significance for initiating treatment in patients with intracranial infections, a finding that is consistent with other studies [25].

Single-agent treatment remains the primary approach in actual clinical practice with a 77%. This may reflect the practical considerations of clinicians when treating postoperative central nervous system infections (CNSIs), such as difficulties in early diagnosis, issues of drug resistance, and individual patient differences [26, 27]. To address these challenges, a multi-faceted research approach is essential. Firstly, advancements in diagnostic technologies, such as rapid genomic sequencing and biomarker identification, could significantly enhance the early and accurate diagnosis of CNSIs [28]. Implementing these technologies in clinical settings would allow for timely and precise treatment interventions, potentially improving patient prognosis [29]. Furthermore, continuous monitoring and follow-up can help in the early detection of any complications or relapses, ensuring timely modifications to the treatment regimen. In conclusion, while single-agent treatment remains prevalent in clinical practice due to practical constraints, the potential of combination therapy to improve outcomes for patients with postoperative CNSIs is significant. Future research that integrates advanced diagnostic tools, personalised medicine, and collaborative efforts will be pivotal in optimising treatment strategies and ultimately enhancing patient care.

Early diagnosis of postoperative CNSIs is challenging, as obtaining cerebrospinal fluid (CSF) specimens relies on invasive procedures like lumbar puncture or external ventricular drainage, and the positive rate of CSF bacterial cultures is low [21]. Therefore, in the absence of microbiological evidence, clinicians tend to adopt broad-spectrum combination therapy to reduce mortality rates [30, 31]. However, with the increasing problem of antibiotic resistance, stricter management policies for antimicrobial agents have been implemented in China, emphasising the importance of rational drug use [32]. When the effects of monotherapy and combination therapy are comparable, monotherapy is preferred to reduce defined daily doses (DDD), which can reduce the bacteria resistance [33]. Thus, not all patients with postoperative CNSIs require immediate combination therapy; treatment should be individualised based on specific clinical conditions. This study also indicated that for moderate to severe postoperative CNSIs, a combination of vancomycin and β-lactam antibiotics with β-lactamase inhibitors may be the optimal regimen, while third- or fourth-generation of cephalosporins are more suitable for mild to moderate CNSIs and step-down therapy.

In addition, the low detection rate of specific pathogens in cerebrospinal fluid (CSF) cultures further complicates the interpretation of the results. In our study, only 13.9% of cases identified specific pathogens, of which gram-positive cocci were the dominant. The initially empirical use of broad-spectrum antibiotics such as meropenem, and ceftriaxone in the absence of definitive microbiological evidence could have masked the actual effectiveness of the treatment regimens. Moreover, because vancomycin was the dominant agent used as an initial empirical treatment, the study did not assess the impact of antibiotic resistance patterns on treatment outcomes, which is a crucial factor in managing postoperative CNSIs. Future research should address these limitations by including prospective, multicentre studies with comprehensive data on pathogen profiles, resistance patterns, and long-term patient outcomes to better inform clinical practice.

Despite the findings of this study, several limitations must be considered in generalising the results. Firstly, the retrospective nature of the cohort study inherently introduces biases related to data collection and patient selection. The reliance on EMR to identify treatment regimens and outcomes may have resulted in misclassification or incomplete data. Furthermore, the study was conducted in a single tertiary hospital, which may limit the generalizability of the findings to other settings with different patient demographics and healthcare practices. The study predominantly focused on initial empirical treatment without considering subsequent modifications based on

culture results or clinical response. This approach may not fully capture the dynamic nature of infection management in clinical practice. The decision to use an SDT or VCT was also influenced by institutional guidelines and individual clinician preferences, which were not accounted for in the analysis.

However, the major advantage of non-randomized studies is their ability to collect data in real-world clinical settings, reflecting actual clinical practices and decisions. This is particularly important when randomised controlled trials (RCTs) are not feasible due to ethical concerns or uncontrollable factors. A significant limitation of non-randomized studies is the presence of selection bias and confounding factors, which can affect the credibility of the results. To mitigate these issues, the propensity score matching (PSM) method was applied in this study to balance differences between the two groups by matching patients' baseline characteristics, thereby providing a more accurate estimate of treatment effects. In this study, matching was performed using a 1:2 ratio and a calliper width of 0.2. The results indicated that although SDT showed plausible practical outcomes for patients with CNSIs, VCT demonstrated superior effectiveness compared to SDT in both unadjusted and adjusted models. Despite this, these methods cannot wholly replace RCTs but provide a strong alternative when RCTs are not feasible. By minimising confounding bias as much as possible, they offer valuable clinical decision-making references.

Conclusion

In conclusion, the findings from this study provide significant insights into the management of postoperative CNSIs in neurosurgical patients. While SDT remains a common treatment approach, particularly for less complex infections, combination therapy (such as VCT) should be considered for more complicated cases due to its superior effectiveness. These results underscore the importance of individualized treatment strategies and the need to consider multiple factors when selecting the most appropriate therapy. Future research that integrates advanced diagnostic tools, personalized medicine, and broader multicentre studies will be essential in optimizing treatment strategies and improving patient care.

Supplementary Information

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Supplementary Material 1

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MY, L and M, W: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing - original draft.L, A; XQ, L; Q, F; QX, S; DF, L; J, W; JH, W: Methodology, Resources, Data curation, Writing - review & editing.SJ, Y: Formal analysis, Data curation, Writing - review & editing.YB, W: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing - original draft, Writing - review & editing.All authors read and approved the final manuscript.

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Data availability
The data used in this study are anonymized patient-level data from the Electronic Medical Records and are not publicly available due to confidentiality concerns. Requests for access to the raw data should be directed to the corresponding author, Yubo Wang at yubow1206@163.com.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from the First Affiliated Hospital Ethics Committee of Xinjiang Medical University (Approval No: K202401-07). In accordance with national regulations "*The Ethical Review of Biomedical Research Involving Humans (2016)*" from the Chinese National Health and Family Planning Commission [17], the need for informed consent was waived as this study used retrospective, anonymized patient data. The waiver was granted by the aforementioned Ethics Committee. Data from patients was anonymized before its use.

Consent for publication
This study contains original, unpublished work and is not being submitted for publication elsewhere. Parts of the results were reported in poster presentations at the following conferences: Wang Y, An L, Li D, and Wang J. *Comparative Effectiveness of Single-Drug Versus Combination Antimicrobial Regimens in Post-Neurosurgical Infections at a Northwest China Hospital*. The 40th International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE), Berlin, Germany, 24–28 August 2024.

Clinical trial
Not applicable.

Competing interests
The authors declare no competing interests.

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