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Original Article

Multidrug-Resistant Pathogens and Outcomes in Post-Neurosurgical Meningitis: A Case Control Study

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Abstract

Objective: Post-neurosurgical meningitis remains a significant challenge, particularly in low-resource settings with a high burden of antimicrobial resistance. This study compared risk factors, microbiological profiles, and clinical outcomes between culture-positive and culture-negative nosocomial meningitis.

Methods: We conducted a case-control study of adults who developed meningitis following neurosurgical procedures at a tertiary care hospital in Karachi, Pakistan (2013–2022). Patients were categorized into culture-positive (cases) and culture-negative (controls). Demographic, clinical, microbiological, and outcome data were collected. Multivariable logistic regression was used to identify factors independently associated with culture-positive meningitis.

Results: Among 85 patients, 46 (54%) were culture-positive. Excision of space-occupying lesions (SOL) was more frequent in culture-negative patients on univariate analysis; however, multivariable regression demonstrated that SOL excision was associated with lower odds of culture-positive meningitis (adjusted OR 0.33; 95% CI: 0.11–0.99; $p = 0.05$). Gram-negative organisms predominated (89%), with multidrug-resistant Acinetobacter baumannii being the most common isolate. Colistin (37.9%) and amikacin (28.3%) showed the highest antimicrobial susceptibility. Clinical outcomes were significantly worse among culture-positive patients, including higher mortality (28.3% vs. 10.3%; $p = 0.05$) and a longer hospital stay (median: 23 vs. 11 days; $p < 0.001$).

Conclusion: Culture-positive post-neurosurgical meningitis is predominantly caused by multidrug-resistant gram-negative organisms and is associated with significantly higher mortality and prolonged hospitalization. Improved diagnostic strategies and antimicrobial stewardship are critical in resource-limited neurosurgical settings.

Keywords: Nosocomial Meningitis, Neurosurgical Infections, Cerebrospinal Fluid, Antimicrobial Resistance, Acinetobacter Baumannii.

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Introduction

In developed countries, nosocomial meningitis accounts for approximately 40% of cases of bacterial meningitis.[1] Nosocomial meningitis is a serious complication of neurosurgical procedures and is associated with significant morbidity, prolonged hospitalization, and considerable mortality.[2] Although diagnostic approaches have advanced, distinguishing postoperative aseptic inflammation from true bacterial meningitis remains challenging, especially when prior antimicrobial exposure lowers cerebrospinal fluid (CSF) culture yield.[3]

In the postoperative period, blood and surgical implant may lead to aseptic meningitis. Cell counts and biochemical parameters (such as protein and glucose levels) measured in cerebrospinal fluid (CSF) have a limited ability to distinguish nosocomial meningitis from postoperative aseptic meningitis.[4] While CSF culture remains the diagnostic gold standard, its yield is often limited due to prior antibiotic exposure.[5] Several neurosurgical factors including ventricular drains, CSF leaks, prolonged surgical duration, repeated procedures, and foreign-body insertion are recognized predictors of central nervous system (CNS) infections.[6-7]

While the microbiological profile traditionally emphasized gram-positive organisms such as *Staphylococcus epidermidis* and *Staphylococcus aureus*, an increasing burden of multidrug-resistant (MDR) gram-negative organisms has emerged,

particularly in resource-limited settings.[8] *Staphylococcal species* account for the majority of isolates in patients with CSF shunt infections, with *Staphylococcus epidermidis* most frequently isolated (47%–64% of infections), followed by *Staphylococcus aureus* (12%–29% of infections).[8-9] The most common isolated gram-negative microorganisms are *Escherichia coli*, *Klebsiella*, *Proteus*, and *Pseudomonas*; cases of *Acinetobacter* meningitis have also been reported in patients with VP shunts.[10]

Crucially, the clinical trajectory of meningitis may differ according to whether a causative organism is identified. Culture-positive cases allow pathogen-directed therapy, whereas culture-negative meningitis often requires broad-spectrum empiric coverage, which may delay appropriate treatment or foster antimicrobial resistance.[11]

Despite the clinical importance of postoperative meningitis, limited data exists comparing culture-positive and culture-negative cases, particularly in low- and middle-income settings with high antimicrobial resistance. This study aims to compare risk factors, microbiological profiles, and clinical outcomes between these two groups in a tertiary care neurosurgical center.

Methods

This retrospective case–control study was conducted at a tertiary care hospital after obtaining approval from the Institutional Ethical Review Committee (ERC No. 2023-8786-25366; informed consent was waived due to the retrospective nature of the study).

Adult patients (≥18 years) who developed meningitis following neurosurgical procedures between January 2013 and December 2022 were included. Nosocomial meningitis was defined as meningitis occurring ≥48 hours after a neurosurgical procedure, characterized by compatible clinical features (fever, neck stiffness, altered mental status, or meningeal signs) along with cerebrospinal fluid (CSF) abnormalities (pleocytosis, elevated protein, and/or decreased glucose), in accordance with established criteria for healthcare-associated meningitis.

Patients were categorized into two groups: cases, defined as those with a positive CSF culture, and controls, defined as those with a negative CSF culture but with clinical and biochemical findings consistent with nosocomial meningitis. Patients with community-acquired meningitis or those without a history of recent neurosurgical intervention were excluded.

Data were collected through review of electronic medical records and patient charts. Variables included demographic characteristics (age, sex), comorbidities, primary neurosurgical diagnosis, and potential risk factors such as external ventricular drain (EVD) placement, ventriculoperitoneal (VP) shunt insertion, lumbar drain use, cerebrospinal fluid leaks, head trauma, skull fractures, and duration of surgery. Clinical features at presentation, laboratory parameters, microbiological findings, treatment modalities (intravenous, intrathecal, and oral antibiotics), and outcomes (mortality, treatment success, and length of hospital stay) were also recorded.

Data were analyzed using STATA version 17. Continuous variables were assessed for normality using the Shapiro–Wilk test. Normally distributed variables were summarized as mean ± standard deviation, whereas non-normally distributed variables were reported as median with interquartile range (IQR). Categorical variables were presented as frequencies and percentages.

For comparisons between cases and controls, the independent sample t-test or Mann–Whitney U test was used for continuous variables, and the chi-square test or Fisher's exact test for categorical variables, as appropriate. Univariate logistic regression analysis was performed to identify factors associated with culture-positive meningitis. Variables with a p-value ≤0.10 or those considered clinically relevant were included in the multivariable logistic regression model. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported. A two-tailed p-value <0.05 was considered statistically significant.

Results

A total of 280 patients were screened, of whom 85 met the inclusion criteria. Among these, 46 (54%) were classified as culture-positive cases and 39 (46%) as culture-negative controls. Both groups demonstrated a male predominance. The median age was comparable between the two groups (cases: 40.5 years [IQR: 34–56] vs. controls: 36 years [IQR: 29–49]).

Hypertension and diabetes were the most common comorbidities. Hypertension was present in 16 (34.8%) cases and 9 (23.1%) controls, while diabetes was observed in 4 (8.7%) cases and 7 (18.0%) controls. These differences were not statistically significant. The most frequently performed neurosurgical procedure was excision of space-occupying lesions (SOL), which was more common in the control group than in cases (43.6% vs. 17.4%; p = 0.01). Other potential risk factors included external ventricular drain (EVD) placement (51.3% in

Table 1: *Comparison of demographics and history of comobitidies*

Variables		Overall N = 85	Nosocomial culture Negative (Control) N = 39	Nosocomial culture Positive (Case) N = 46	p-value
Age	Mean (SD)	42.3±14.5	39.6±15.1	44.2±13.6	0.14
	Median (IQR)	40 (31 – 51)	36 (29 – 49)	40.5 (34 – 56)	
Gender	Male	60 (70.6)	27 (69.2)	33 (71.7)	0.80
	Female	25 (29.4)	12 (30.8)	13 (28.3)	
Comorbidities	Diabetes	11 (12.9)	7 (18.0)	4 (8.7)	0.33
	Hypertension	25 (29.4)	9 (23.1)	16 (34.8)	0.24
	Chronic Kidney Disease	3 (3.5)	2 (5.1)	1 (2.2)	0.59
	No prior co-morbid	54 (63.5)	27 (69.2)	17 (58.7)	0.32
	Intracranial bleed	1 (33.3)	0 (0.0)	1 (50.0)	1.00
	Hypothyroid	1 (33.3)	0 (0.0)	1 (50.0)	
	Tuberose sclerosis	1 (33.3)	1 (100.0)	0 (0.0)	
	Neurosurgical Intervention	85 (100.0)	39 (100.0)	46 (100.0)	-
	Longer duration procedure	13 (15.3)	9 (23.1)	4 (8.7)	0.08
	CSF rhinorrhea	1 (20.0)	0 (0.0)	1 (25.0)	1.00
	Post procedure CSF	1 (20.0)	0 (0.0)	1 (25.0)	
Interval between surgery and onset of symptoms (days)		9 (6 – 15)	7 (5 – 14)	9.5 (6 – 20)	0.69

controls vs. 32.6% in cases) and a longer duration of surgery (23.1% vs. 8.7%), both showing borderline statistical significance (p = 0.08). Figure 1A, B

Fever was the most common presenting symptom, reported in 76.1% of cases and 66.7% of controls. Other clinical features, including headache, seizures, low Glasgow Coma Scale (GCS), and CSF leak, were comparable between the two groups, with no statistically significant differences. Table 2

Blood cultures were performed in 66 patients. Among these, positive growth was identified in 4 (13.3%) controls and 2 (5.6%) cases, with no statistically significant difference (p = 0.39).

CSF analysis was available for 81 (95.3%) patients. There were no significant differences between the two groups in CSF protein, glucose, white blood cell count, neutrophil predominance, or lymphocyte count. Among the 46 culture-positive cases, bacterial pathogens accounted for the majority of isolates (89.1%, n = 41), while fungal pathogens constituted 10.9% (n = 5). Multidrug-resistant (MDR) *Acinetobacter baumannii* was the most frequently isolated organism, identified in 35.6% of cases. Among culture-positive isolates, colistin demonstrated the highest sensitivity (37.9%), followed by amikacin (28.3%) for *Acinetobacter*. Overall susceptibility to other antibiotics was low, reflecting a high burden of multidrug-resistant organisms. Figure 2

All patients received intravenous antibiotics. Adjunctive therapies were more frequently used in culture-positive patients, with 16 (34.8%) receiving intrathecal antibiotics and 6 (13.0%) receiving oral therapy, both of which were statistically significant compared to controls (p < 0.05).

The overall mortality rate was 20% (n = 17). Mortality was higher among culture-positive cases compared to controls (28.3% vs. 10.3%), with borderline statistical significance (p = 0.05). The length of hospital stay was significantly longer in the culture-positive group, with a median duration of 23 days (IQR: 12–35.5) compared to 11 days (IQR: 6.0–19.0) in the control group (p < 0.001). Table 1 shows the detailed comparison of demographic features, signs and symptoms, laboratory parameters, treatment and outcomes of patients between the two groups.

On univariate analysis, excision of SOL and length of hospital stay were significantly associated with

Table 2: *Comparison of Sign & Symptoms and laboratory parameters.*

Variables		Overall N = 85	Nosocomial culture Negative (Control) N = 39	Nosocomial culture Positive (Case) N = 46	p-value
Signs and Symptoms	Fever	61 (71.8)	26 (66.7)	35 (76.1)	0.34
	Headache	13 (15.3)	8 (20.5)	5 (10.9)	0.24
	Seizures	8 (9.4)	4 (10.3)	4 (8.7)	1.00
	Low GCS	32 (37.7)	15 (38.5)	17 (37.0)	0.89
	Wound Discharge	11 (12.9)	6 (15.4)	5 (10.9)	0.75
	CSF leak	12 (14.1)	8 (20.5)	4 (8.7)	0.13
	Neck stiffness	1 (20.0)	1 (33.3)	0 (0.0)	
	Neck symptoms	1 (20.0)	0 (0.0)	1 (50.0)	1.00
	Vomiting	3 (60.0)	2 (66.7)	1 (50.0)	
Whole blood analysis	TLC (x 10E9/L)	12.9 ± 4.9	13.6 ± 5.3	12.4 ± 4.6	0.27
	CRP (mg/L)	11 (1.9 – 36)	16.7 (4.9 – 45)	5.5 (1.6 – 28.4)	0.66
	Blood culture done	66 (77.6)	32 (82.1)	37 (80.5)	0.98
	No Growth	60 (90.9)	26 (86.7)	34 (94.4)	0.39
	Growth	6 (9.1)	4 (13.3)	2 (5.6)	
CSF Analysis	Segregation	81 (95.3)	37 (94.9)	44 (95.7)	
	CSF Protein (mg/dl)	145 (80 – 232)	165 (111 – 231)	108 (69 – 230)	0.92
	CSF Glucose (mg/dl)	46.5 (20 – 79)	50 (28 – 78)	38 (10.5 – 80)	0.29
	CSF WBC (x 10E9/L)	0.23 (0.04 – 0.96)	0.28 (0.08 – 1.45)	0.20 (0.03 – 0.45)	0.62
	CSF Neutrophils	70 (32 – 80)	65 (32 – 80)	70 (40 – 90)	0.35
	CSF Lymphocytes	30 (15 – 60)	30 (16 – 60)	30 (10 – 60)	0.71
	CSF Culture	85 (100.0)	39 (100.0)	46 (100.0)	-
Culture outcomes	Bacteria	41 (89.1)	0 (0.0)	41 (89.1)	-
	Fungal	5 (10.9)	0 (0.0)	5 (10.9)	

SD: standard deviation; IQR: interquartile range; SOL: space occupying lesion; EVD: extra-ventricular drain; VP: ventriculoperitoneal; CSF: cerebrospinal fluid; GCS: Glassgow coma scale; TLC: total leukocyte count; CRP: C-reactive protein; WBC: white blood cells

culture-positive meningitis. In multivariable logistic regression, excision of space-occupying lesion was associated with lower odds of culture-positive nosocomial meningitis (OR = 0.33, p = 0.05), indicating a borderline statistically significant protective association. Length of hospital stay was also independently associated with culture-positive status (adjusted OR: 1.06; 95% CI: 1.02–1.11; p = 0.002). Table 4 presents the results of both univariate and multivariate analyses.

Discussion

This study provides a decade of data on post-neurosurgical meningitis in a high-volume LMIC tertiary center, highlighting the predominance of MDR gram-negative pathogens and significant morbidity associated with culture-positive infections.

According to the past literature, the most common predisposing factors for nosocomial meningitis were invasive CNS procedures, traumatic brain injury, basal skull fracture, brain hemorrhage or use of invasive CNS devices.[12-14] While several studies have explored the risk factors and outcomes of meningitis following neurosurgical interventions, there is a notable scarcity of research focused on comparing culture-positive and culture-negative nosocomial

Table 3: *Comparison of therapy and outcomes between case-control groups*

Variables		Overall N = 85	Nosocomial culture		p-value
			Negative (Control) N = 39	Positive (Case) N = 46	
Route of therapy	Intravenous	85 (100.0)	39 (100.0)	46 (100.0)	-
	Intrathecal	16 (18.8)	0 (0.0)	16 (34.8)	<0.001
	Oral	6 (7.1)	0 (0.0)	6 (13.0)	0.03
Outcomes	Treatment successful	65 (76.5)	31 (79.5)	34 (73.9)	0.55
	Treatment failed	2 (2.4)	0 (0.0)	2 (4.4)	0.5
	Death	17 (20.0)	4 (10.3)	13 (28.3)	0.05
	Discharged	49 (57.7)	26 (66.7)	23 (50.0)	0.12
	Hospital stay (Days)	16.5 (8.0 – 16.5)	11 (6.0 – 19.0)	23 (12 – 35.5)	<0.001

Table 4: *Regression analysis*

Variables	Univariate			Multivariable		
	OR	95% CI	p-value	OR	95% CI	p-value
Excision of SOL	0.27	0.10 – 0.73	0.01	0.33	0.11 – 0.99	0.05
Length of hospital stay	1.07	1.03 – 1.11	0.001	1.06	1.02 – 1.11	0.002

OR: odd ratio; CI: confidence interval; SOL: space occupying lesion

meningitis.[14] This aligns with recent literature, where invasive neurosurgical procedures have been identified as major risk factors for postoperative meningitis due to their complexity and potential for contamination of the cerebrospinal space.[15] Around one-third of cases arise during the first week post-surgery, with an additional third presenting in the second week following the procedure.[1] In our study, patients undergoing excision of SOL demonstrated reduced odds of nosocomial meningitis; however, the borderline statistical significance suggests that larger studies are needed to confirm this finding. The observed protective association may reflect confounding factors such as case selection or surgical characteristics rather than a true protective effect.

In recent studies positive CSF cultures, especially with gram-negative organisms, were associated with poor outcomes and higher mortality.[12,16] A study from Spain reported 51 cases of *Pseudomonas aeruginosa* growth in cerebrospinal fluid following surgical procedures, with a mortality rate of approximately 33.3%.[17] Kizilates et al. reported significantly higher 14-day (p = 0.022) and 30-day mortality rates (p = 0.023) in cases involving gram-negative nosocomial meningitis.[2] In our study, 17 patients (20%) died from nosocomial meningitis, with higher mortality observed in the group with positive CSF cultures, where 13 out of 17 patients (76%) died due to the infection.

The predominance of MDR gram-negative organisms in our cohort is consistent with emerging global trends in post-neurosurgical infections, particularly in low- and middle-income countries. Recent studies have highlighted *Acinetobacter baumannii* as a leading pathogen, often associated with limited therapeutic options and high mortality.[18] In a recent cohort study, MDR *A. baumannii* infections were identified as one of the most severe complications following neurosurgical procedures, with challenges in achieving microbiological clearance and limited effective antibiotics.[19] Our findings, with 89% gram-negative isolates and a high prevalence of MDR *A. baumannii*, further support this epidemiological transition.

The higher mortality observed among culture-positive patients in our study aligns with previous literature demonstrating worse outcomes in microbiologically confirmed infections, particularly those caused by gram-negative organisms. A large institutional study reported mortality rates of up to 40.3% in post-neurosurgical *Acinetobacter* meningitis, significantly higher than other etiologies.[20] Another comparative study demonstrated mortality rates exceeding 50% in *Acinetobacter*-associated meningitis compared to approximately

24% in non-*Acinetobacter* or culture-negative cases.[21] In contrast, our study observed a mortality rate of 28.3% in culture-positive patients, which, although lower, still reflects the substantial burden associated with MDR infections in neurosurgical settings.

The association between neurosurgical devices and infection risk has been consistently reported in the literature. External ventricular drains (EVDs), in particular, have been identified as independent predictors of poor outcomes and increased mortality in post-neurosurgical meningitis.[20] In our study, EVD placement showed a trend toward higher frequency in culture-negative cases; however, this did not reach statistical significance. This discrepancy may reflect differences in patient selection, timing of infection, or antibiotic exposure prior to culture sampling.

A substantial proportion of patients in our study were culture-negative, highlighting a well-recognized limitation in the diagnosis of post-neurosurgical meningitis. Previous studies have reported culture-negative rates of approximately 40–45% in similar populations.[21] Factors contributing to negative cultures include prior antibiotic exposure, low bacterial load, biofilm-associated infections, and limitations of conventional microbiological techniques. This highlights the need for advanced diagnostic modalities such as polymerase chain reaction (PCR) and metagenomic sequencing, which have shown improved pathogen detection in central nervous system infections.

An observational study reported a median hospital stay of 38 days and a mean average ICU stay of 18 ± 12 days.[12] A study of pediatric patients admitted to U.S. hospitals with meningitis reported a median hospital stay of 14 days.[22] In a cohort study of 144 adult patients, Panic et al. reported a median hospital stay of 27 days.[23] In comparison, our median hospital stay of 23 days in culture-positive patients reflects a substantial healthcare burden, although shorter than some reported series, possibly due to differences in case severity and institutional practices.

The high prevalence of MDR organisms in our cohort has important therapeutic implications. Recent studies have explored the role of intrathecal or intraventricular antibiotic administration, particularly polymyxins and tigecycline, in improving outcomes in MDR gram-negative meningitis. For instance, combined intravenous and intraventricular polymyxin therapy has been associated with improved clinical and microbiological outcomes in patients with resistant infections.[24] Similarly, intrathecal tigecycline has demonstrated higher microbiological clearance rates compared to intravenous therapy alone.[19] The increased use of intrathecal antibiotics in culture-positive patients in our study reflects this evolving therapeutic approach.

Interestingly, excision of space-occupying lesions (SOL) was associated with lower odds of culture-positive meningitis in our study. However, this finding should be interpreted with caution. It is possible that this association reflects residual confounding, differences in surgical complexity, or variations in perioperative antibiotic use rather than a true protective effect. Larger prospective studies are required to validate this observation.

This study provides a decade-long analysis of post-neurosurgical meningitis from a high-volume tertiary care center in a low- and middle-income country, offering valuable insights into the evolving microbiological spectrum and antimicrobial resistance patterns in this setting. The comparative evaluation of culture-positive and culture-negative cases adds clinical relevance by addressing a common diagnostic dilemma in neurosurgical practice. Additionally, the inclusion of detailed clinical, microbiological, and outcome data allows for a comprehensive assessment of factors associated with disease severity and prognosis.

However, certain limitations should be acknowledged. The single-center design may limit the generalizability of the findings to other institutions with different patient populations and infection control practices. The retrospective nature of the study introduces the possibility of selection and information bias, including incomplete documentation and unmeasured confounders. The relatively small sample size may have limited the statistical power to detect significant associations for some variables. Furthermore, the lack of advanced diagnostic modalities, such as molecular assays or metagenomic sequencing, may have contributed to the high proportion of culture-negative cases. Data on prior antibiotic exposure and standardized severity scoring were also not consistently available, which could influence both culture yield and clinical outcomes.

The findings of this study are particularly relevant to low- and middle-income countries, where the burden of antimicrobial resistance is disproportionately high. Limited access to advanced diagnostics, suboptimal infection control practices, and widespread empirical antibiotic use contribute to the emergence of MDR pathogens in neurosurgical units. Our results highlight the urgent need for region-specific antimicrobial stewardship programs and infection control interventions. Future research should focus

on integrating molecular diagnostic techniques to improve pathogen detection, evaluating standardized treatment protocols for MDR infections, and identifying modifiable risk factors to reduce infection rates. Multicenter prospective studies are needed to better define optimal management strategies for both culture-positive and culture-negative post-neurosurgical meningitis.

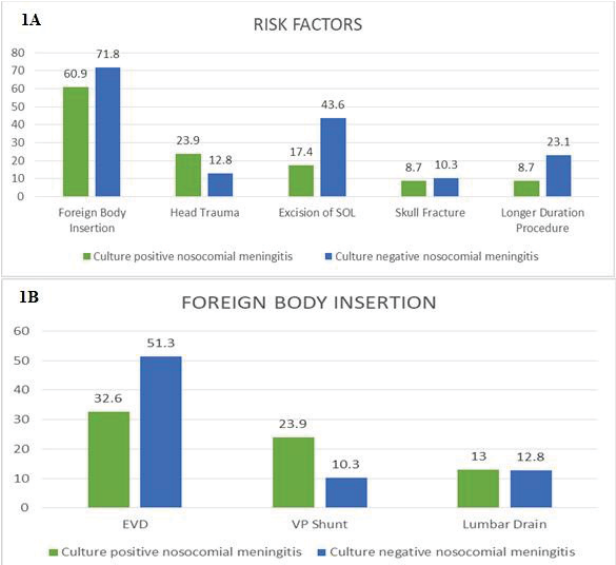

Figure 1A: *Common risk factors amongst cases and controls.*

Figure 1B: *Types of foreign body insertion in culture positive and culture negative organisms.*

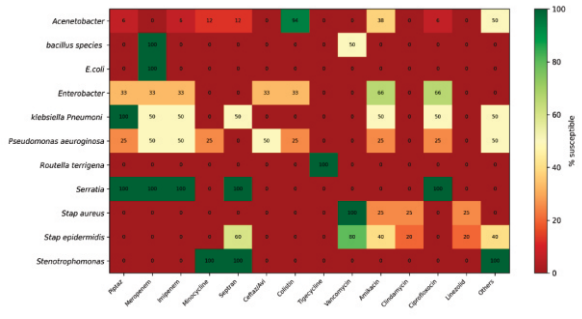

Figure 2: *Heat map showing antimicrobial susceptibility patterns of microorganisms isolated from ICU patients.*

Conclusion

Culture-positive post-neurosurgical meningitis is associated with multidrug-resistant gram-negative pathogens and worse clinical outcomes. The high proportion of culture-negative cases highlights limitations in conventional diagnostics. Future studies incorporating molecular diagnostics and standardized infection control strategies are essential to improve patient outcomes in neurosurgical settings.

Ethical Approval: The IRB/EC approved this study via letter no. ERC No. 2023-8786-25366 dated July 01, 2023.

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Authors' Contribution

FI: Conception.

IK,NN: Design of the work.

SB, SMS, SS: Data acquisition, analysis, or interpretation.

FI, SB, SMS, SS: Draft the work.

IK, NN: Review critically for important intellectual content.

All authors approve the version to be published.

All authors agree to be accountable for all aspects of the work.

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