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ORIGINAL WORK

Risk, Predictive, and Preventive Factors for Noninfectious Ventriculitis and External Ventricular Drain Infection

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Abstract

Background: External ventricular drain (EVD) is used for monitoring intracranial pressure or diverting cerebrospinal fluid. However, confirmation of an infection is not immediate and requires obtaining culture results, often leading to the excessive use of antibiotics. This study aimed to compare noninfectious ventriculitis and EVD infection in terms of the risk factors, predictors, prognosis, and effectiveness of care bundle interventions.

Methods: This retrospective study was conducted at a medical center with 1,006 beds in northern Taiwan between January 2018 and July 2022. Standard EVD insertion protocols and care bundles have been implemented since 2018, along with the initiation of chlorhexidine.

Results: In total, 742 EVD cases were identified. Noninfectious ventriculitis typically presents with fever approximately 8 days following EVD placement, whereas EVD infection typically manifests as fever after 20 days. Aneurysmal subarachnoid hemorrhage was strongly associated with the development of noninfectious ventriculitis (adjusted odds ratio [OR] 2.6, 95% confidence interval [CI] 1.5–4.4). Alcoholism (adjusted OR 3.5, 95% CI 1.1–12.3) and arteriovenous malformation (adjusted OR 13.1, 95% CI 2.9–58.2) significantly increased the risk of EVD infection. The EVD infection rate significantly decreased from 3.6% (14 of 446) to 1.0% (3 of 219) ($p = 0.03$) after the implementation of chlorhexidine gluconate bathing.

Conclusions: Aneurysmal subarachnoid hemorrhage or fever with neuroinflammation within 2 weeks of EVD placement is indicative of a higher likelihood of noninfectious ventriculitis. Conversely, patients with arteriovenous malformation, alcoholism, or fever with neuroinflammation occurring after more than 3 weeks of EVD placement are more likely to necessitate antibiotic treatment for EVD infection. Chlorhexidine gluconate bathing decreases EVD infection.

Keywords: Ventriculitis, External ventriculostomy drain, Antibiotics, Chlorhexidine gluconate bathing, Needle-free connector

Introduction

An external ventricular drain (EVD) is used to monitor intracranial pressure or divert cerebrospinal fluid (CSF) in acute hydrocephalus, intraventricular hemorrhage, subarachnoid hemorrhage, ventriculitis, and severe traumatic brain injury. Incidence rates of EVD-related infections range from 5 to 23% owing to diverse definitions, each related to its specific clinical practice [1–3]. A positive CSF culture result is an essential criterion, combined with CSF pleocytosis,

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low CSF glucose levels, and clinical symptoms, such as fever, meningeal signs, or changes in consciousness [4, 5]. Because of the unavailability of immediate culture results, it is impossible to differentiate noninfectious ventriculitis from EVD infection at the first instance. In clinical practice, once fever and changes in consciousness occur in patients with EVD, preemptive antibiotics are often prescribed before the final CSF culture results are obtained. This often leads to the excessive use of antibiotics, contributing to issues such as antibiotic resistance. To date, there are insufficient studies on the topic, and a solid consensus on this topic is unavailable [5].

Longer duration of EVD placement, increased frequency of CSF sampling, intraventricular hemorrhage, skull fracture, CSF leakage, systemic infection, and underlying conditions such as diabetes, alcoholism, and cigarette smoking may elevate the risk of EVD infection [3, 6–9]. However, study identifies specific risk and predictive factors for EVD infection but does not address noninfectious ventriculitis. Sweid et al. observed that the mean CSF output was higher in patients with EVD infection [8]. Further investigation into this phenomenon may assist clinicians in detecting and responding to the disease at an earlier stage. Nevertheless, preventive EVD care bundles are more important in decreasing EVD-related complications. Clinical practice guidelines strongly recommend periprocedural prophylactic antibiotics and antimicrobial-impregnated drains and strongly discourage prolonged use of antibiotics [5]. However, only 53% of institutions use antibiotic-impregnated catheters, and 55% use prolonged prophylactic systemic antibiotics [4]. Moreover, one study has suggested daily CSF sampling [6], whereas another recommended reducing the sampling frequency [10] to reduce EVD infection rate. Additional research is required to identify the most cost-effective and implantable interventions.

The objective of this study was to analyze clinical risk factors and predictors for both noninfectious ventriculitis and EVD infection. This includes examining the timing of fever following EVD placement and the daily trend of EVD output leading up to the onset of fever. Additionally, a comparison was conducted between patients diagnosed with ventriculitis who received antibiotic treatment for less than or more than 1 week to determine which individuals may be suitable for conservative management without antibiotics. Finally, the effectiveness of a new care bundle intervention including chlorhexidine gluconate bathing in reducing EVD infections was evaluated.

Methods

Patient Population

This study was conducted at a medical center with 1,006 beds in northern Taiwan. The study was approved by the Taipei Medical University Joint Institutional Review Board (TMU-JIRB approval number: N202210032; approval date: November 1, 2022). The requirement for informed consent was waived given the negligible risks involved in a standard-of-care observational study. The protocols adhered to the ethical guidelines set forth by the responsible committees overseeing human experimentation in each hospital as well as the Declaration of Helsinki 1975. This study retrospectively analyzed all patients who underwent EVD insertion between January 2018 and July 2022. This was a retrospective chart review of patient demographics, surgical diagnosis, medical comorbidities, CSF analysis results, EVD CSF daily output, EVD type and indwelling sites, lengths of intensive care unit (ICU) and hospital stay, modified Rankin scale score, and survival status at 180 days after discharge.

This study defined EVD infection as fever (> 37.5 °C) after EVD placement [11], CSF pleocytosis (CSF white blood cell [WBC] count > 100/mm^3) determined from combined CSF sampling during the fever episode, ratio of CSF to serum glucose level < 0.5, and positive CSF Gram stain and culture results during the EVD indwelling period [12]. Noninfectious ventriculitis was defined according to the previously mentioned criteria, including negative CSF Gram stain or culture results, and physicians also considered a lower likelihood of true infection or opted for early discontinuation of antibiotics. The exclusion criteria were (1) age < 18 years; (2) systemic infection or preexisting central nervous system infection, such as brain abscess or meningitis, before or during EVD placement; (3) positive CSF culture result without clinical symptoms, CSF leukocytosis, or decreased CSF glucose level; and (4) CSF WBC to red blood cell ratio < 500, which may indicate traumatic tapping. We modified the definition of alcoholism based on the guidelines provided by the National Institute on Alcohol Abuse and Alcoholism. In our definition, alcoholism is characterized by alcohol consumption exceeding 14 standard drinks per week for men or more than 7 standard drinks per day for women.

EVD Insertion Protocol, Care Bundles, and Modification

All EVDs were inserted after complete hair shaving, sterile draping of the head, and full-body draping in the operating room. All patients received prophylactic periprocedural antibiotics with intravenous cefazolin for 24 h or clindamycin for those with a history of beta-lactam antibiotic allergy. The catheter was tunneled for at least 5 cm. Standard nonimpregnated catheters were

used in all cases. In clinical practice, to regulate intracranial pressure in patients and maintain it at a normal level of 10 cm H_2O, a height of 10 cm above the tragus is used as the EVD exit point to allow excessive CSF drainage. As CSF appearance improves, attempts may be made to elevate the drainage position to 15 or 20 cm before removing the EVD.

We measured the CSF output hourly, changed the dressing every 3 days, strictly maintained the closed system, and replaced the collecting bag when it was full. In the case of system obstruction, a trial flushing was performed using a standard aseptic technique with normal saline to relieve the obstruction. CSF sampling was based on the clinical suspicion of EVD infection (i.e., fever, neurological degradation, and changes in serum C-reactive protein levels or total WBC counts). Once fever and ventriculitis were confirmed, intravenous antibiotics were administered until CSF pleocytosis and the ratio of CSF to serum glucose levels normalized. CSF data were collected before initiating empiric antibiotics for EVD infection.

Since 2021, our modified EVD care bundles include the following: (1) changing the CSF sampling site from a proximal three-way connector to a needle-free Y-connector distal to the collector and (2) applying 2% chlorhexidine gluconate bathing for all ICU patients on the first day of admission and every other day during their ICU stay. Pretreatment involved eight disposable wipes completely soaked in 2% chlorhexidine gluconate. Subsequently, four wipes were applied to each of the four limbs, and another four were applied to the neck-to-chest, abdomen-to-groin, back-to-buttocks, and intended site of surgery.

Statistical Analysis

Differences in patient characteristics between the two groups were compared using Pearson's χ^2 test for categorical variables and Student's *t*-test for continuous variables. Linear regression or logistic regression was used to calculate 95% confidence interval (CI) for mean difference (MD) and odds ratio (OR) between noninfectious ventriculitis and non-ventriculitis as well as between EVD infection and non-ventriculitis. Trend plots were predicted from the estimation of a fractional polynomial of EVD CSF daily output, and the resulting curve was plotted along with 95% CI of the mean. All statistical tests were performed using Stata software (version 14.0; StataCorp, College Station, TX).

Results

In total, 753 patients with EVD were assessed for eligibility. Seven patients with brain abscesses, three with tuberculous meningitis, and one with cryptococcal meningitis were excluded (Supplementary Fig. 1). Seven hundred forty-two patients with EVD (mean age 61.4 years, male 48.8%, cigarette smoking 30.6%, alcoholism 17.1%, diabetes mellitus 31.4%) were enrolled for analysis. Primary underlying pathologies were intracranial hemorrhage (46.9%), aneurysmal subarachnoid hemorrhage (30.9%), brain tumor (14.2%), arteriovenous malformation (4.6%), and trauma (7.7%) (Table 1).

ORs for Noninfectious Ventriculitis and EVD Infection

The noninfectious ventriculitis and EVD infection groups included 62 (8.4%) and 18 (2.4%) patients, respectively. Aneurysmal subarachnoid hemorrhage accounted for 29% in the non-ventriculitis group, 54.8% in the noninfectious ventriculitis group, and 16.7% in the EVD infection group. Patients with aneurysmal subarachnoid hemorrhage were more likely to develop noninfectious

Table 1 Patient characteristics

	No. of cases
Categories, *n* (%)	
No ventriculitis	662 (89.2)
Noninfectious ventriculitis	62 (8.4)
External ventricular drain infection	18 (2.4)
Basic profiles	
Age, mean (SD)	61.4 (15.4)
BMI, mean (SD)	24.6 (4.7)
Male, *n* (%)	362 (48.8)
Smoking, *n* (%)	227 (30.6)
Alcoholism, *n* (%)	127 (17.1)
GCS before surgery, median (IQR)	11 (8)
Comorbidities, n (%)	
Type 2 diabetes mellitus	233 (31.4)
Hypertension	563 (75.9)
Coronary artery disease	178 (24.0)
Congestive heart failure	13 (1.8)
Ischemic stroke	106 (14.3)
Chronic obstructive pulmonary disease	16 (2.2)
Chronic kidney disease	103 (13.9)
Chronic liver disease	116 (15.6)
Surgical diagnosis, n (%)	
Intracranial hemorrhage	347 (46.9)
Aneurysmal subarachnoid hemorrhage	229 (30.9)
Brain tumor	105 (14.2)
Arteriovenous malformation	34 (4.6)
Trauma	57 (7.7)
Stroke	26 (3.5)
Skull fracture	13 (1.8)
Cerebrospinal fluid leak	3 (0.4)

BMI Body mass index, *GCS* Glasgow coma scale, *IQR* Interquartile range

ventriculitis (adjusted OR 2.6, 95% CI 1.5–4.4) than other groups. However, alcoholism and arteriovenous malformations accounted for 17.5% and 4.4% of the non-ventriculitis group, 8.1% and 1.6% of the noninfectious ventriculitis group, and 38.7% and 22.2% of the EVD infection group, respectively. Alcoholism (adjusted OR 3.5, 95% CI 1.1–12.3) and arteriovenous malformation (adjusted OR 13.1, 95% CI 2.9–58.2) significantly increased EVD infection (Table 2).

Regarding intrathecal injection with urokinase or recombinant tissue plasminogen activator, 26 patients (3.9%) without ventriculitis and three patients (4.7%) with noninfectious ventriculitis received the procedure (OR 1.2, 95% CI 0.3–4.0); none of the patients exhibited EVD infection (Supplementary Table 1). A sensitivity analysis excluding patients who received intrathecal medications showed no change in significant factors, such as alcoholism and surgical diagnosis (Supplementary Table 2).

EVD Indwelling Duration and Mean Diagnosis Day

The average EVD indwelling time was 12.7 ± 1.2 days. Patients with CSF leak had a significantly longer EVD indwelling time of 17.3 ± 3.4 days ($p = 0.002$), and patients with brain tumor had a significantly shorter EVD indwelling time of 11.6 ± 1.5 ($p = 0.026$) (Supplementary Table 3). The mean diagnosis day after EVD placement was 8.5 ± 5.1 days for noninfectious ventriculitis and 24.1 ± 7.2 days for EVD infection (MD 14.5, 95% CI 8.1–22.7) (Table 3). Compared with EVD placement time of < 14 days, EVD placement for > 14 days exhibited a significantly higher EVD infection rate (0.5% vs. 6.6%, respectively; $p < 0.001$) and noninfectious ventriculitis rate (6.2% vs. 13.7%, respectively; $p = 0.001$) (Table 4).

EVD Volumes After Placement and Before Fever

For patients without ventriculitis or infection, average daily CSF outputs from EVD were 91.8 ± 3.7 mL/day on day 1, 164.2 ± 3.8 mL/day on day 2, 167.0 ± 3.8 mL/day on day 3, 160.5 mL/day on day 4, and 162.4 ± 4.0 mL/day on day 5 and gradually decreased to 153.6 ± 4.0 mL/day and 148.1 ± 4.2 mL/day on days 6 and 7, respectively (Supplementary Fig. 3a). The EVD daily CSF outputs before the development of fever in culture-negative patients were 154.1 ± 15.2 mL/day 1 day before fever, 163.1 ± 15.2 mL/day 2 days before fever, and 162.6 ± 15.2 mL/day 3 days before fever. The EVD daily CSF outputs before fever developed in patients with EVD infection were 136.1 ± 28.1 mL/day 1 day before fever, 129.3 ± 28.1 mL/day 2 days before fever, and 125.2 ± 28.1 mL/day 3 days before fever (Supplementary Fig. 3b).

Table 2 ORs for noninfectious ventriculitis and external ventricular drain infection

	Noninfectious ventriculitis OR (95% CI)		External ventricular drain infection OR (95% CI)	
	Univariable analysis	Multivariable analysis[a]	Univariable analysis	Multivariable analysis[a]
Basic profiles				
Sex, male	1.3 (0.8–2.1)	0.7 (0.4–1.4)	0.5 (0.2–1.3)	0.4 (0.1–1.3)
Smoking	0.7 (0.4–1.3)	0.9 (0.4–1.8)	1.0 (0.4–3.0)	0.4 (0.1–1.6)
Alcoholism	0.4 (0.2–1.0)	0.4 (0.1–1.0)	3.9 (1.2–13.1)*	3.5 (1.1–12.3)*
Comorbidities				
Type 2 diabetes mellitus	0.9 (0.5–1.5)	0.9 (0.5–1.7)	0.3 (0.1–1.2)	0.4 (0.1–1.20)
Hypertension	1.4 (0.7–2.6)	1.6 (0.8–3.2)	1.1 (0.4–3.5)	1.3 (0.3–5.2)
Coronary artery disease	1.0 (0.6–1.9)	1.0 (0.5–1.9)	1.2 (0.4–3.5)	1.5 (0.4–6.2)
Ischemic stroke	0.5 (0.2–1.3)	0.5 (0.2–1.3)	1.2 (0.3–4.0)	1.0 (0.2–4.0)
Chronic kidney disease	0.8 (0.3–1.7)	0.9 (0.4–2.2)	0.8 (0.2–3.3)	0.6 (0.1–3.1)
Chronic liver disease	0.8 (0.4–1.7)	0.9 (0.4–2.0)	1.1 (0.3–3.7)	1.1 (0.3–4.3)
Surgical diagnosis				
Intracranial hemorrhage	0.6 (0.3–0.9)	1.0 (0.4–2.0)	0.8 (0.2–2.7)	0.6 (0.2–2.2)
Aneurysmal subarachnoid hemorrhage	3.0 (1.8–5.0)**	2.6 (1.5–4.4)**	0.3 (0.1–1.1)	0.2 (0.1–0.9)
Brain tumor	0.4 (0.1–1.0)	0.6 (0.2–2.0)	0.3 (0.1–3.1)	0.3 (0.1–2.8)
Arteriovenous malformation	0.4 (0.1–2.7)	0.8 (0.4–1.3)	10.2 (2.5–42.6)**	13.1 (2.9–58.2)**
Practice change				
After bundle care vs. before	0.8 (0.5–1.4)	0.8 (0.4–1.3)	0.3 (0.1–1.1)	0.3 (0.2–0.8)*

CI Confidence interval, *OR* Odds ratio

*$p < 0.05$; **$p < 0.01$

[a] Multivariable analysis involves incorporating all the factors listed in the table into regression analysis

Table 3 Outcomes of noninfectious ventriculitis and external ventricular drain infection

	Non-ventriculitis	Noninfectious ventriculitis	EVD infection
Diagnosis day			
Days (SD)	–	8.7 (5.1)	24.1 (7.2)
Mean difference (95% CI)	–	Reference	15.4 (8.1 to 22.7), $p<0.001$
EVD indwelling time			
Days (SD)	12.5 (1.3)	17.5 (4.5)	37.5 (8.3)
Mean difference (95% CI)	Reference	5.0 (− 3.8 to 13.8), $p=0.263$	25.0 (9.3 to 40.7), $p=0.002$
Length of intensive care unit stay			
Days (SD)	10.1 (0.7)	14.6 (2.5)	25.0 (4.7)
Mean difference (95% CI)	Reference	4.4 (− 0.2 to 6.6), $p=0.059$	14.9 (6.6 to 23.1), $p<0.001$
Length of hospital stay			
Days (SD)	31.8 (0.8)	36.0 (4.8)	68.6 (8.9)
Mean difference (95% CI)	Reference	4.2 (− 1.7 to 10.1), $p=0.163$	36.7 (26.1 to 47.4), $p<0.001$
VP shunt dependence			
No. of cases	199 (30.1%)	23 (37.1%)	8 (44.4%)
Odd ratios (95% CI)	Reference	1.4 (0.8 to 2.4), $p=0.252$	1.9 (0.7 to 4.8), $p=0.197$
mRS score during discharge			
mRS scores (SD)	4.0 (0.1)	3.7 (0.5)	4.4 (1.0)
Mean difference (95% CI)	Reference	− 0.3 (− 0.7 to 0.1), $p=0.197$	0.4 (− 0.3 to 1.2), $p=0.238$
In-hospital mortality			
No. of cases	108 (16.3%)	6 (9.8%)	2 (11.1%)
Odd ratios (95% CI)	Reference	0.6 (0.2 to 1.3), $p=0.186$	0.6 (0.1 to 2.8), $p=0.553$

CI Confidence interval, *EVD* External ventricular drain, *mRS* modified Rankin Scale, *VP shunt* ventriculoperitoneal shunt

Outcomes of Noninfectious Ventriculitis and EVD Infection

Among the non-ventriculitis, noninfectious ventriculitis, and EVD infection groups, the EVD indwelling times were 12.5 ± 1.3, 17.5 ± 4.5 (MD 5.0, 95% CI − 3.8 to 13.8), and 37.5 ± 8.3 (MD 25.0, 95% CI 9.3–40.7) days; the lengths of ICU stay were 10.1 ± 0.7, 14.6 ± 2.5 (MD 4.4, 95% CI − 0.2 to 6.6), and 25.0 ± 4.7 (MD 14.9, 95% CI 6.6–23.1) days; and the lengths of hospital stay were 31.8 ± 0.8, 36.0 ± 4.8 (MD 4.2, 95% CI − 1.7 to 10.1), and 68.6 ± 8.9 (MD 36.7, 95% CI 26.1–47.4) days, respectively (Table 5).

Characteristics of Antibiotic Durations: < 7 Versus > 8 Days in Noninfectious Ventriculitis

In patients with noninfectious ventriculitis, antibiotics were discontinued once physicians confirmed the absence of true infection and observed the normalization of CSF pleocytosis and the ratio of CSF to serum glucose levels. In this group, 13 (19.7%) patients used antibiotics for < 7 days, and 53 (80.3%) patients received antibiotics for > 8 days. Patients who received antibiotics for < 7 days were significantly younger than those who were received antibiotics for > 8 days (49.7 ± 4.7 vs. 65.8 ± 1.9 years, $p<0.001$), and the incidence of diabetes mellitus was also significantly lower in this group (0% vs. 35.9%, $p=0.013$) (Table 5). The initial CSF WBC count and neutrophil percentage were 309 ± 68.1/mm^3 and 57.1% ± 6.0% for antibiotics administered for < 7 days and 1,163.2 ± 520.8/mm^3 and 93.0% ± 28.1% for antibiotics administered for > 8 days (Table 5).

Effectiveness of Modified EVD Care Bundles

From 2021, we modified the EVD care bundles. The EVD infection rate significantly decreased from 3.6% (14 of 446) to 1.0% (3 of 219) ($p=0.03$). However, the noninfectious ventriculitis rate decreased from 9.0% (40 of 446) to 7.4% (22 of 219) without significance ($p=0.50$) (Fig. 1).

Discussion

This study included 742 EVD cases, with 8.4% noninfectious ventriculitis and 2.4% EVD infection. Aneurysmal subarachnoid hemorrhage is more likely to lead to noninfectious ventriculitis, whereas arteriovenous malformation, alcoholism, and EVD placement for > 14 days significantly increase EVD infection. For patients with noninfectious ventriculitis and EVD infection, the CSF output from patients with EVD persistently increased before fever for 1 week. Compared with non-ventriculitis and noninfectious ventriculitis, EVD infection significantly increased the length of ICU and hospital stays. Ventriculoperitoneal shunt dependence, modified Rankin

Table 4 Patient characteristics comparison based on EVD indwelling duration

	EVD indwelling time < 14 days	EVD indwelling time ≥ 14 days	*p* value
No. of cases (%)	467 (62.4)	281 (37.6)	
EVD days	8.0 (17.1)	21.7 (49.3)	< 0.001
Basic profiles			
Age, mean (SD), years	61.0 (15.4)	61.9 (15.4)	0.423
BMI, mean (SD)	24.5 (4.6)	24.9 (4.9)	0.172
Male, *n* (%)	235 (50.3)	148 (52.7)	0.546
Smoking, *n* (%)	145 (31.1)	82 (29.2)	0.623
Alcoholism, *n* (%)	73 (15.6)	54 (19.2)	0.228
GCS before surgery, Mean (SD)	10.8 (3.8)	10.6 (3.7)	
Comorbidities, n (%)			
Hypertension	351 (75.2)	215 (76.5)	0.725
Coronary artery disease	116 (24.8)	63 (22.4)	0.480
Congestive heart failure	11 (2.4)	2 (0.7)	0.147
Cerebral vascular accident	69 (14.8)	38 (13.5)	0.667
Chronic obstructive pulmonary disease	12 (2.6)	4 (1.4)	0.435
Chronic kidney disease	69 (14.8)	35 (12.5)	0.386
Chronic liver disease	87 (18.6)	30 (10.7)	0.004
Diabetes mellitus	148 (31.7)	86 (30.6)	0.807
Surgical diagnosis, *n* (%)			
Intracranial hemorrhage	213 (45.6)	134 (48.0)	0.544
Aneurysmal subarachnoid hemorrhage	136 (29.1)	93 (33.1)	0.287
Brain tumor	76 (16.3)	30 (10.7)	0.039
Arteriovenous malformation	20 (4.3)	14 (5.0)	0.718
Trauma	40 (8.6)	17 (6.1)	0.255
Stroke	20 (4.3)	6 (2.1)	0.150
Skull fracture	10 (2.1)	3 (1.0)	0.390
Cerebrospinal fluid leak	2 (0.4)	1 (0.4)	1.000
Complication, *n* (%)			
Non-infectious ventriculitis	19 (6.2)	36 (13.7)	0.001
External ventricular drain infection	2 (0.5)	16 (6.6)	< 0.001

BMI Body mass index, *EVD* External ventricular drain, *GCS* Glasgow coma scale

scale score at discharge, and in-hospital mortality were not significantly different among patients with no ventriculitis, noninfectious ventriculitis, and EVD infection. Finally, our study demonstrates the effectiveness of changing the CSF sampling site from a proximal three-way connector to a needle-free Y-connector distal to the collector and chlorhexidine gluconate bathing.

In clinical practice, upon obtaining a bacterial culture report, differentiation between noninfectious ventriculitis and EVD infection can guide us to avoid antibiotic overuse. However, a negative CSF culture result requires at least a 10-day observation period [13]. Before bacterial culture reports are obtained, most physicians or surgeons usually prescribe preemptive antibiotics. Minimizing antibiotic overtreatment for noninfectious ventriculitis helps decrease antibiotic resistance and side effects. Previous research has demonstrated that CSF cytokines, such as interleukin-6, interleukin-8, and tumor necrosis factor-α, and metabolomics play crucial roles in distinguishing inflammation from infection [14]. Rapid pathogen detection using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry may be a promising method for the rapid diagnosis of EVD bacterial infections [15]. Our data found that the mean diagnosis day after EVD placement was 8.5 ± 5.1 days for noninfectious ventriculitis and 24.1 ± 7.2 days for EVD infection. Therefore, fever approximately 8 or 20 days after EVD placement may provide hints to differentiate between these two conditions.

For noninfectious ventriculitis, although the first culture results were negative, many physicians continued antibiotics while CSF inflammation persisted. At our institution, we discontinued antibiotics only after the culture was negative and CSF inflammation subsided.

Table 5 Antibiotics durations for noninfectious ventriculitis

	Noninfectious ventriculitis with antibiotics for ≤ 7 days	Noninfectious ventriculitis with antibiotics for > 8 days	*p* value
No. of cases (%)	13 (19.7)	53 (80.3)	
Basic profiles			
Age, mean (SD), years	49.7 (4.7)	65.8 (1.9)	0.001
Male, *n* (%)	5 (38.5)	22 (41.5)	1.000
Body mass index, mean (SD)	24.8 (0.7)	26.2 (1.7)	0.412
Smoking, *n* (%)	6 (45.2)	10 (18.9)	0.067
Alcoholism, *n* (%)	1 (7.7)	4 (7.5)	1.000
Diabetes mellitus, *n* (%)	0 (0)	19 (35.9)	0.013
GCS before surgery, mean (SD)	11.0 (0.9)	10.6 (0.5)	0.701
Ventriculitis profiles			
Fever, mean (SD), ℃	38.7 (0.1)	38.4 (0.2)	0.158
CSF WBC count, mean (SD), cells/mm^3	309 (68.1)	1,163.2 (520.8)	0.423
CSF neutrophil, mean (SD), %	57.1 (6.0)	93.0 (28.1)	0.528
CSF lymphocyte, mean (SD), %	19.7 (4.3)	16.4 (2.2)	0.498
CSF RBC, mean (SD), cells/mm^3	23,403.7 (6,521.8)	100,298.5 (31,174.0)	0.229
CSF protein, mean (SD), mg/dL	109.8 (19.1)	206.2 (44.8)	0.295
CSF glucose, mean (SD), mg/dL	52.1 (4.0)	78.4 (5.0)	0.014
Blood glucose, mean (SD), mg/dL	130.5 (10.1)	197.7 (10.1)	0.002
CSF to blood glucose level ratio	0.4 (0.1)	0.4 (0.1)	0.735
Surgical diagnosis, *n* (%)			
Intracranial hemorrhage	6 (46.2)	17 (32.1)	0.351
Aneurysm subarachnoid hemorrhage	8 (61.2)	30 (56.6)	1.000
Brain tumor	0 (0)	4 (7.5)	0.577
Arteriovenous malformation	1 (7.7)	0 (0)	0.197
Outcome, mean (SD)			
EVD indwelling time, days	18.7 (3.1)	17.3 (1.0)	0.556
Intensive care unit stay, days	12.2 (3.3)	15.0 (1.5)	0.417
Hospital stay, days	30.6 (6.7)	36.7 (2.1)	0.250
VP shunt dependence, %	6 (46.5)	21 (39.6)	0.757
mRS score during discharge	2.9 (0.5)	3.9 (0.2)	0.054
In-hospital mortality, %	1 (7.7)	5 (9.6)	1.000

CSF Cerebrospinal fluid, *EVD* External ventricular drain, *GCS* Glasgow coma scale, *mRS* modified Rankin Scale, *RBC* Red blood cell, *VP shunt* Ventriculoperitoneal shunt, *WBC* white blood cell

For younger patients without diabetes mellitus, antibiotics were more likely to be prescribed for < 7 days. A lower initial CSF WBC count and neutrophil percentage were also predictors of shorter antibiotic duration.

Low-grade fever is generally identified as a body temperature within the range of 37.5 to 38.3 °C. A study conducted by Affronti et al. revealed that within the group of patients with low-grade fever, there is no apparent association between body temperature values and the severity of underlying diseases, and the etiological spectrum remains consistent [11]. To avoid underestimating the risk of EVD infection, patients with low-grade fever have been included in the cohort analysis. For patients without ventriculitis or infection, the average daily CSF output from the EVD peaked at days 2–5 after EVD placement. However, EVD daily CSF output before development of fever in culture-negative patients with EVD infection was persistently elevated for at least 1 week, which was also mentioned in a previous study [8]. Thus, a persistently high CSF output of > 150 mL/day for > 5 days may imply neuroinflammation, and clinicians can respond in a timely manner in such situations.

Clinical practice guidelines recommend several strategies, such as periprocedural prophylactic antibiotics and antimicrobial-impregnated drains, to reduce EVD infections [5]. For the past few years, several trials have shown the effects of chlorhexidine gluconate bathing in reducing central-line-associated bloodstream infection [16,

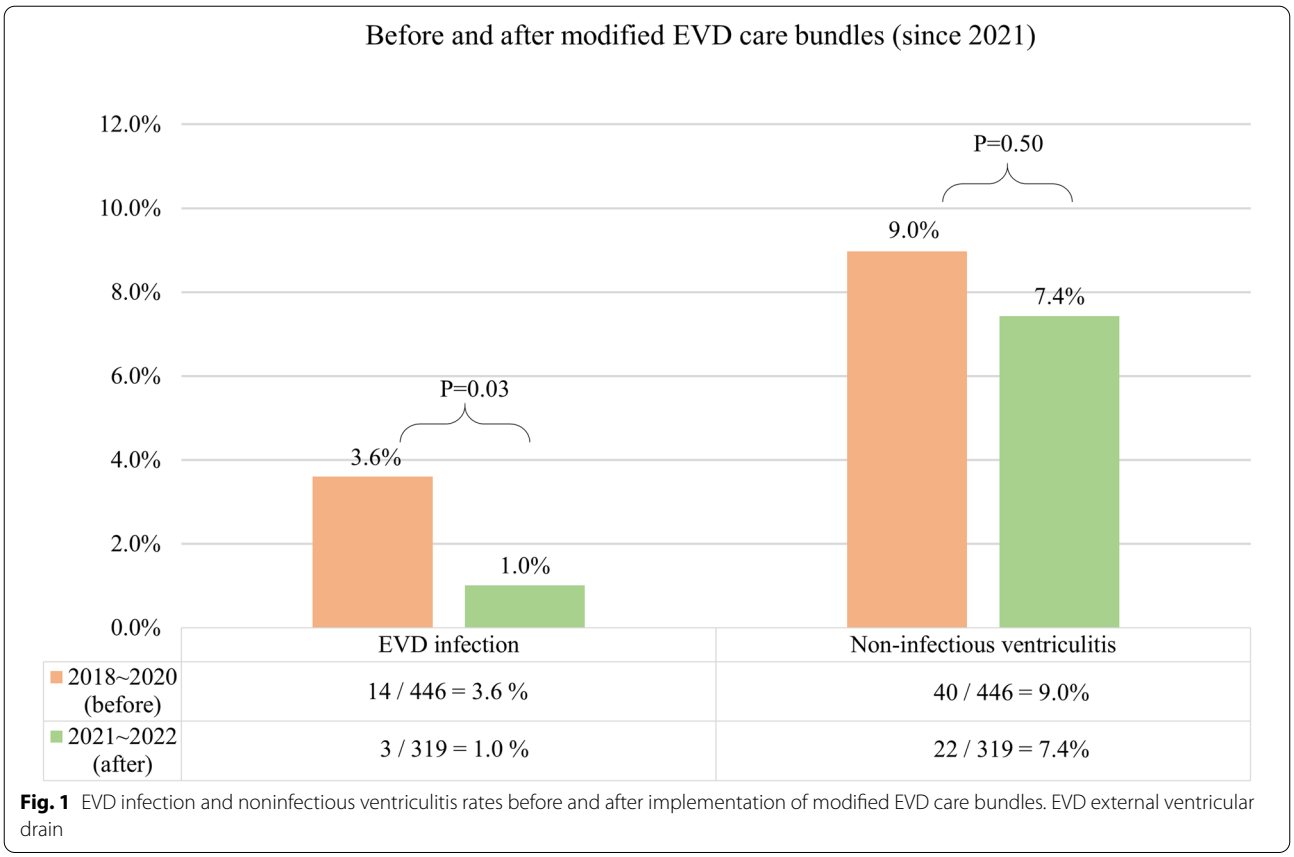

Fig. 1 EVD infection and noninfectious ventriculitis rates before and after implementation of modified EVD care bundles. EVD external ventricular drain

17] and surgical site infection [18]. Smaller studies have revealed that needle-free or needleless connectors, rather than traditional three-way hubs, also decreased bloodstream infection [19–21]. In our experience, we adopted chlorhexidine gluconate bathing and CSF sampling using needleless connectors and largely decreased EVD infection, whereas noninfectious ventriculitis, which is more likely related to surgical conditions, such as aneurysmal subarachnoid hemorrhage, did not decrease. However, we incorporated chlorhexidine gluconate bathing and changed the CSF sampling site from a proximal three-way connector to a needle-free Y-connector located distal to the collector in our revised bundle care. As a result, it is difficult to determine which factor is more significant in reducing EVD infections. A study conducted by Kinast et al. [22] compared CSF collection through the proximal and distal port below the overflow system from an EVD. The study found that CSF supernatant from the overflow system can be effectively used for diagnostic workup, including various biochemical parameters commonly required in numerous clinical conditions [22]. Our hospital's standard care procedure entails placing EVDs in the operating room and includes complete hair shaving. However, it is important to note that this practice may not be universally applicable to the global patient population because there is no standardized procedure followed worldwide.

To our knowledge from literature research, this is the largest cohort study to evaluate patients with indwelling EVDs and the first study to analyze noninfectious ventriculitis regarding characteristics, predictors, trends of daily CSF output from EVD, and antibiotic duration. This study provides insights into the early recognition of EVD inflammation characterized by persistently elevated CSF output and conservative antibiotic strategies in patients with noninfectious ventriculitis. Our study has some limitations. First, it is important to acknowledge that this study was conducted at a single center with a small sample size; however, the use of a uniform protocol enhanced the cleanliness of the data. Second, distinguishing between noninfectious ventriculitis and true EVD infection may pose challenges during the initial stages. We collected CSF data before initiating empiric antibiotics to reduce the risk of false negative for EVD infection. In our study, it was discovered that among patients with fever and ventriculitis, only 22.5% had EVD infections requiring antibiotic use. Other patients who may clinically appear to have ventriculitis might be subjected to

excessive antibiotic use. Future research could focus on describing and studying noninfectious ventriculitis, aiming to reduce antibiotic usage and mitigate the development of antibiotic resistance.

Conclusions

The occurrence of EVD infection had a significant impact on prolonging the length of ICU stay and overall hospitalization duration. CSF outputs from EVD reached their peak at approximately 2 days after EVD placement but consistently increased for 1 week prior to the development of fever and neuroinflammation. In the case of younger patients with aneurysmal subarachnoid hemorrhage, the presence of fever and neuroinflammation within 2 weeks of EVD placement indicates a higher likelihood of noninfectious ventriculitis, which can be managed conservatively by either refraining from antibiotic usage or employing a shorter duration of antibiotic treatment. Conversely, patients with arteriovenous malformation, alcoholism, diabetes, extremely high CSF WBC counts, or fever accompanied by neuroinflammation occurring after more than 3 weeks of EVD placement are more likely to require antibiotic treatment for EVD infection.

Supplementary Information

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Author Contributions

T-FH, Y-KS, and C-HT conceptualized and designed the study. I-CS, W-TC, H-WL, C-ML, I-HK, Y-CL, and Y-KT critically revised the manuscript and provided essential intellectual contributions. All authors read and approved the final version of the manuscript for publication.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical Approval/Informed Consent

Ethical clearance for this research was obtained from the Institutional Review Board of Taipei Medical University Joint Institutional Review Board (approval number: N202210032; approval date: November 1, 2022).

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