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Indicators of external ventricular drainage-related infections—a retrospective observational study

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Abstract
Background External ventricular drainage (EVD) is frequently used in different groups of patients in neurocritical care. Despite the frequent use of EVD, no consensus regarding the diagnosis of EVD-related infection currently exists, and diagnosis is commonly based on criteria for the diagnosis of non-EVD-related CNS infections. This study evaluates the diagnostic accuracy of clinical and laboratory parameters for the prediction of EVD-related infection in patients with proven EVD-related infection.
Methods In two tertiary care centers, data on EVD insertions were matched with a microbiologic database of cultured microorganisms and positive Gram stains of cerebrospinal fluid (CSF) to identify patients with EVD-related infections. Available clinical data and results of blood tests and CSF analysis were retrospectively collected. Predefined potential clinical and laboratory predictors of EVD-related infection were compared between three time points: at the time EVD insertion and 48 h before and at the time of occurrence of EVD-related infection.
Results Thirty-nine patients with EVD-associated infection defined by positive CSF culture or positive CSF Gram stains and concomitant clinical signs of infection were identified. At the time of infection, a significantly higher incidence of abnormal temperature, high respiratory rate, and a slightly but significantly higher incidence of decreased mental state were observed. The assessed blood and CSF parameters did not significantly differ between the different assessment time points.
Conclusions Our analysis of 39 patients with culture positive EVD-related infection showed that commonly used clinical and laboratory parameters are not reliable infection predictors.

Keywords EVD infection · Diagnostic parameters · Markers of inflammation · CSF analysis

Introduction

External ventricular drainage (EVD) catheters are frequently used for the detection and management of elevated intracranial pressure (ICP). EVD allows accurate intracranial pressure monitoring and offers ICP control by temporarily draining cerebrospinal fluid (CSF). In neurocritical care, EVD is used in various disease states, but primarily in patients with subarachnoid (SAH) or intracerebral hemorrhage (ICH) or traumatic brain injury (TBI) [1].

The incidences per 100,000 person-years range from 3–25 for SAH [2–5], 16–33 for ICH [6–8], and 200–530 for TBI [9–11]. A substantial proportion of these patients will require placement of an EVD catheter for appropriate treatment. Infection of the EVD catheter and subsequently of the intra- and periventricular space is one of the major complications of EVD placement [12]. The reported rates for EVD-related infections range from 2 % to more than 27 % in different studies [12–17]. EVD-related infection has been related to higher morbidity and mortality and prolonged need of intensive care resources [18]. Despite the fact that optimal management of EVD-related infections is relevant for patient outcomes, no consensus on optimal prophylaxis, diagnosis, and treatment exists [12, 19].

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Diagnosis of EVD-related infection is commonly based on well-established criteria for the diagnosis of non-EVD-related CNS infections [20]. Rapidly available parameters for the diagnosis of central nervous system (CNS) infections include clinical signs such as fever, nuchal rigidity, and a change in mental status as well as blood tests such as elevated white blood cell (WBC) count, neutrophilia with a shift towards immature band forms, or elevated serum C-reactive protein (CRP) and procalcitonin (PCT) levels [21]. However, in neurocritical care patients, clinical signs of central nervous system infection can be masked by the low level of consciousness due to the underlying condition or the treatment with sedative drugs. Additionally, blood tests are non-specific, in that they may indicate infections of sites other than the CNS or be elevated due to causes not related to an infection. Analysis of CSF for EVD-related infection usually includes parameters determined by CSF WBC count. In patients suffering from SAH, ICH, or TBI—the most frequent indications for EVD placement—CSF is frequently contaminated with blood, and CSF-WBC-based parameters may therefore be misleading. Additionally, the presence of blood in the CSF space can induce a sterile inflammation and mimic infection [22]. Positive cerebrospinal fluid (CSF) Gram stain and culture represent the gold standard for the diagnosis of an EVD-related infection [19, 23]. However, Gram stains are often negative even in culture-positive CSF [24] and CSF cultures take several days until bacterial growth can safely be excluded and do not allow early diagnosis of infection.

The aim of this study was to assess changes of clinical and laboratory parameters potentially indicating an EVD-related infection in patients suffering from SAH, ICH, or TBI. Using subsequent positive CSF culture or Gram stain as an indicator for the occurrence of EVD-related infection, our study aims to evaluate changes in clinical and laboratory parameters during the time from EVD insertion to occurrence of possible sterile inflammation in the CSF space and subsequently to the time of proven EVD-related infection. Additionally, the diagnostic accuracy of clinical and laboratory parameters for the prediction of EVD-related infection was to be established.

Materials and methods

Study design Retrospective observational study in two tertiary center critical care units.

Patients We reviewed all available medical records of all adult patients older than 16 years of age in whom an EVD was inserted over a period of 5 years at the University Hospital Berne, Switzerland (center 1), and over 7 years at the Royal North Shore Hospital of Sydney, Australia (center 2). All neurosurgical procedure protocols during the study period were screened for insertion of an EVD. Patient records were matched with the microbiologic database of all cultured microorganism in CSF and all positive Gram stains of CSF to identify patients with EVD-related infections during the course of the patients' hospital stay. Patients who presented with a primary CNS infection on admission were excluded.

Data collection Baseline characteristics include patient demographics, diagnosis, Glasgow Coma Score (GCS), Hunt & Hess [25] and Fisher [26] grading systems for SAH and ICH score [27] for intra-cerebral hemorrhage at ICU admission, duration of ICU and hospital stay, duration of EVD in place, survival at hospital discharge, Glasgow Outcome Score, and modified Rankin Score. Clinical data included the following parameters: clinical signs of a systemic inflammatory response syndrome (SIRS) (temperature >38.3 °C or <36 °C, heart rate >90 beats/min, respiratory rate >20 breaths/min or $PaCO_2 < 32$ mmHg), and of CNS infection (nuchal rigidity, headache, and changes in mental status). Signs of CNS infection were rated as absent if ongoing sedation did not allow for conclusive assessment. Surveillance CSF samples were routinely collected and blood tests performed on a daily or alternate-day basis in both institutions in patients with EVDs as a part of standard clinical management. The following parameters were extracted from the laboratory database: red blood (RBC) count, blood WBC count, serum CRP level, CSF RBC count, CSF WBC count, CSF Gram stain and CSF culture, and results of cultures of any removed EVD. All available clinical and laboratory parameters, starting from the day of EVD insertion until day 3 after the occurrence of EVD-related infection, were collected and included in the study database for analysis.

Definition of EVD-related infection According to the NHSN/CDC definition of healthcare-associated meningitis [23, 28], an EVD-related infection is defined as a positive CSF culture or identification of bacteria on Gram stain at least 24 h after placement of an EVD with clinical signs of infection. Coagulase-negative staphylococci (CoaNS) were considered to be contaminated if further clinical or biochemical abnormalities were absent.

Evaluated potential predictors of EVD-related infection Evaluated potential predictors consisted of CSF and blood laboratory results and clinical signs of central nervous system infection: blood WBC count, percentage of blood WBC band forms, serum CRP levels, CSF cell count, CSF RBC/WBC ratio, CSF cell index, presence of positive SIRS criteria, and clinical sings of CNS infection. A positive cell count was defined as a CSF WBC/RBC ratio >0.01. Cell Index was calculated as the ratio of leukocytes to erythrocytes in CSF divided by leukocytes to erythrocytes in peripheral blood, according to Beer et al. [12] Clinical and laboratory parameters of three different time points during the period of EVD

placement were included for further analysis. Firstly, at the time of EVD insertion (T_{EVD})—representing a state of absence of EVD-related infection and sterile inflammation; secondly 48 h before occurrence of EVD-related infection (T_{-2d})—representing a state of absence of EVD-related infection but possible presence of sterile inflammation caused by the presence of blood in the CSF space; and lastly, at the time of positive CSF culture (T_{inf}).

Statistical analysis Data is presented as mean (standard deviation) for parametric and median (quartiles) for non-parametric data. Normal distribution was established using D'Agostino & Pearson omnibus normality test. For comparison of categorical variables at different time points Chi-square test was applied. One-way repeated-measurement ANOVA was used to compare continuous parameters indicative of EVD infection at the different predefined time points. Mauchly's test was used to assess whether the data violate the assumption of sphericity, in which case Greenhouse–Geisser correction was applied. All statistical analyses were performed using IBM SPSS Statistics 20 and GraphPad Prism Version 6.01.

Results

We identified and reviewed the medical records of 20 patients in center 1 and 32 patients in center 2 with positive CSF cultures and concomitant EVD insertion after searching microbiological databases and matching them with the registered adult patients with an EVD. A total of ten patients were excluded from the analysis because CSF infection was present at the time of EVD insertion or because sufficient clinical data was not available. In three patients, coagulase-negative staphylococci were present in the CSF sample at the time of EVD insertion while further clinical or biochemical abnormalities were absent. These results were considered to be contaminants and the patients were excluded from further analysis (Fig. 1). Thirty-nine patients with EVD-associated infection were included in the final analysis. Patient characteristics are shown in Table 1. The majority of patients had suffered from a subarachnoid hemorrhage ($n=20$). At the time of EVD placement, 31 of 39 patients were mechanically ventilated and two patients were diagnosed with non-EVD-related infections, whereas at the time of diagnosis of EVD infection, 20 of 39 patients were mechanically ventilated and in 14 patients non-EVD infections were diagnosed. In 38 patients, cultures of CSF were positive for bacterial growth; in one patient, bacteria were identified on CSF Gram stain, whereas the CSF culture remained negative. In 16 patients, Gram stain was negative, despite positive cultures, and in five patients Gram stain had not been performed. A total of 12 different bacteria were cultured and four cultures grew two different species of bacteria. Compared to patients in which CSF cultures grew one organism, or patients in which one class of bacteria were identified on CSF Gram stain, patients in which cultures grew two organisms did not significantly differ regarding survival ($p=1.0$) or length of stay in ICU ($p=0.292$) or in hospital ($p=0.08$). In 13 patients, CSF samples were positive for coagulase-negative staphylococcus and were associated with at least one clinical and biochemical sign of inflammation.

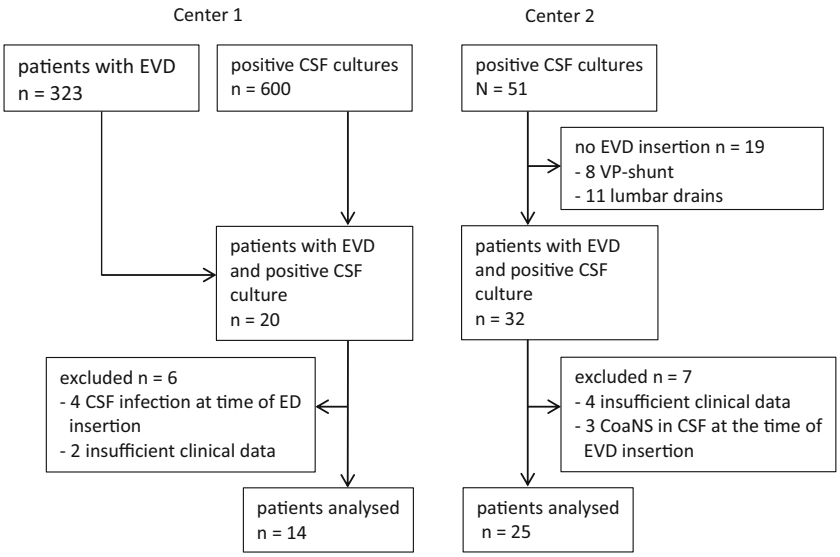

Fig. 1 Study flow chart. In center 1, EVD insertions in a total of 323 patients were included in the surgical database while concomitantly 600 positive CSF cultures and/or CSF Gram stains were registered during the study period. In center 2, a total of 51 positive CSF cultures and/or Gram stains were identified in a registry containing all neurosurgical patients and respective microbiological data. After exclusion of patients with CSF drainage by other means than EVD, patients in whom CNS infection was present at the time of EVD insertion and patients with insufficient data documentation, a total of 39 patients were included for further analysis

Table 1 Patient characteristics

Parameter	*n*
Gender (male/female)	17/22
Diagnosis	
SAH	20
TBI	9
Tumor	3
AVM	2
ICH	5
Neurological findings at the time of EVD insertion	
GCS 13–15	14
GSS 9–12	5
GCS < 8	18
Hunt and Hess (median)	3
Fisher (median)	4
ICU length of stay (days)	16.6 ± 11.9
Survival (yes/no)	32/7
EVD days before infection (days)	9.7 ± 6.6
Cultured organism	
Coagulase-negative staphylococci	13
Enterococcus faecalis	4
Enterobacter sp.	2
Staphylococcus aureus	4
Staphylococcus haemolyticus	1
Klebsiella pneumoniae	2
Escherichia coli	1
Serratia marcescens	2
Acinetobacter spp	7
Pseudomonas aeruginosa	3
Sphingomonas paucimobilis	1
Bacillus	1
Gram stain	
Gram-negative rods	7
Gram-positive cocci	8
Gram-negative cocci	2
Gram-negative and positive rods	1
Negative	16
Not available	5

AVM arteriovenous malformation; *EVD* external ventricular drainage; *GCS* Glasgow Coma Scale; *ICH* intracerebral hemorrhage; *ICU* intensive care unit; *SAH* subarachnoid hemorrhage; *TBI* traumatic brain injury

At the time of infection occurrence, a significantly higher incidence of abnormal temperature increased respiratory rate, and a slight but significantly higher incidence of decreased mental state were observed. However, at each time point, a substantial proportion of patients received sedating drugs, and therefore the occurrence of headache, nuchal rigidity, and a decrease in mental status were not reliably determinable (Table 2). The assessed blood parameters, blood WBC count, percentage of WBC band forms, and levels of CRP, did not

Table 2 Frequencies of occurrence of clinical signs of EVD-related infection at different time points

	T_{EVD}	T_{-2d}	T_{inf}	*p* value
Temperature >38.3 or <36°	7 (18 %)	14 (36 %)	19 (49 %)	0.016
Heart rate >90/min	8 (21 %)	13 (33 %)	15 (38 %)	0.209
Respiratory rate >20/min	2 (5 %)	9 (23 %)	12 (31 %)	0.014
Nuchal rigidity	1 (3 %)	2 (5 %)	1 (3 %)	0.772
Decrease mental state	1 (3 %)	5 (13 %)	9 (23 %)	0.041
Headache	2 (5 %)	4 (10 %)	7 (18 %)	0.193
Use of sedative drugs	17 (44 %)	15 (38 %)	19 (49 %)	0.659

EVD external ventricular drainage; T_{EVD} time point of EVD insertion; T_{-2d} time point 2 days before occurrence of EVD infection, T_{inf} time point of EVD infection

significantly differ between the assessment time points. CSF analysis revealed 11 of 39 patients with normal CSF cell counts (less than four cells M/l) and 17 of 39 patients with normal ratio of CSF WBC/RBC (<0.01) on the day of positive CSF culture. It was only in 16 cases that we observed increasing CSF pleocytosis. In 15 cases, an increase in CSF WBC/RBC ratio and in 13 cases an increase in cell index was

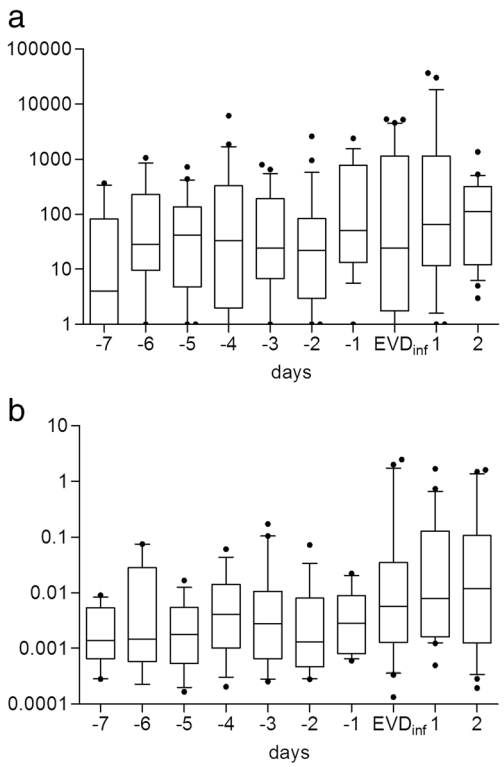

Fig. 2 **a** CSF WBC stratified by days before and after occurrence of EVD infection. The CSF white blood cell count of patients stratified in days before and after occurrence of EVD-related infection features a very high inter-individual variability. **b** CSF Cell Index stratified by days before and after occurrence of EVD infection. The CSF cell index of patients stratified in days before and after occurrence of EVD-related infection feature a very high inter-individual variability

Table 3 Comparison of blood and CSF parameters indicative of EVD-related infection at different time points

	T_{EVD}	T_{-2d}	T_{inf}	F-ratio	*p* value
Blood WBC	13.0 [10.6–17.6]	12.3 [10.0–14.9]	15.1 [10.3–17.9]	3.46	0.057
Blood % band forms	10 [9–16]	10 [6–11]	10 [7–14]	3.41	0.064
Serum CRP	29 [6–74]	15 [1–39]	20 [6–57]	0.55	0.529
CSF WBC count	18 [2–258]	22 [5–92]	55 [2–1142]	3.13	0.053
CSF WBC/RBC ratio	0.0035 [0.0011–0.017]	0.0043 [0.0014–0.035]	0.0165 [0.0016–0.1107]	9.84	0.132
CSF cell index	0.0012 [0.0003–0.0043]	0.0012 [0.0003–0.0061]	0.0031 [0.0002–0.0316]	3.30	0.087

CRP C-reactive protein, *CSF* cerebrospinal fluid, *EVD* external ventricular drainage; *p* significance value, T_{EVD} time point of EVD insertion, T_{-2d} time point 2 days before occurrence of EVD infection, T_{inf} time point of EVD infection, *WBC* white blood cell count

documented. The assessed CSF parameters featured a high inter-individual variability during the time period of EVD placement (Fig. 2a, b). The differences in CSF parameters at the different assessment time points did not reach statistical significance (Table 3).

Discussion

In our retrospective analysis, we identified 39 patients with culture-proven EVD-related infections in a period of 5 years in two university hospitals. Our results indicate that none of the commonly used blood and CSF parameters of EVD-related infection significantly differed between the three analyzed time points—the time of EVD insertion, 48 h before occurrence of EVD-related infection, representing a state of absence of EVD-related infection but possible presence of sterile inflammation and at the time of culture-proven CSF infection. At the time of EVD infection, a significantly higher incidence of abnormal temperature increased respiratory rate and decreased mental state was noted.

Our study adds information about the development over time of cell counts and indices in CSF in a substantial cohort of patients with culture-proven EVD-related infection. We can show that in a large proportion of patients, CSF cell counts as well as indices remain unchanged despite clinically suspected and culture-proven EVD-related infection. The incidence of EVD-related infections of 8 % in our cohort and spectrum of bacterial pathogens cultured is consistent with earlier observations [19, 29, 30]. The study limitations mainly consist of the retrospective nature of the data collection and the lack of controls with similar baseline characteristics without infection.

Timely diagnosis and appropriate treatment is of importance for improving the outcome of patients with EVD-related infections. Positive CSF cultures, along with clinical signs and suspicion of an infection, are considered to allow the diagnosis of EVD-related infection with high specificity [23]. However, CSF culture results are only available with significant delay and their sensitivity might be impaired by concomitant antibiotic treatment. Many clinicians therefore rely on readily available parameters based on CSF white and red cell count when suspecting EVD-related infection [19]. However, in the context of SAH, ICH, or TBI, the presence of blood in the CSF might represent a major confounder for CSF blood cell counts. Although CSF-WBC is routinely used to diagnose EVD-related infections, there is insufficient data to support this approach [31]. The CSF cell index has been introduced to account for the dilution effect of CSF hemorrhage on the increase of CSF-WBC. The CSF cell index has shown promising results for the diagnosis of EVD-related infection in a prospective study with 13 patients with EVD [32]. The sample size of this cohort was small and patients had a very high EVD infection rate of >50 %. To date, only sensitivity and specificity of a few single diagnostic parameters have been reported in the literature [33, 34]. Studies comparing changes of CSF parameters over time in the context of sterile inflammation due to the intra-ventricular presence of blood versus changes caused by EVD-related infections are scarce [35]. This information might be important for enabling the correct interpretation of CSF results.

Our data suggests that commonly used clinical and laboratory parameters including those based on CSF blood cell counts are not sufficiently sensitive and specific to be the basis for diagnosis and treatment decisions. Recent studies suggest a role for different cytokines and biomarkers measured in CSF in the diagnosis of EVD-related infection [36, 37]. However, before being implemented in the clinical routine, these findings have to be confirmed in larger studies.

We conclude that routine analysis of CSF samples to screen patients for EVD-related infection does not seem to be justified. In our cohort analysis of CSF samples in patients with EVD-related infection, CSF parameters were not indicative of infection. Therefore, even in the context of a high suspicion of EVD infection, CSF analysis might not offer reliable additional information to decide if antibiotic treatment should be started. In our institutions, we start empiric antibiotic treatment for EVD infection based on an individual assessment

of patient characteristics and clinical and laboratory findings indicative for EVD- and non-EVD-related infection. If CSF cultures remain negative, antibiotic treatment is discontinued. In the future, larger prospective cohort studies of patients with EVD should be performed to further investigate the accuracy of diagnostic markers of EVD-related infections.

Compliance with ethical standards

Funding No funding was received for this research.

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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Comment

In this retrospective analysis, collaborators from two intensive care units identified patients with confirmed EVD-associated CSF infection. This was defined by a positive CSF culture or Gram stain as well as clinical signs of infection.

Even though these patients had proven CSF infection, the authors failed to find any statistically significant difference in CSF parameters when tested at different time points. While this does not prove the absence of a difference, it does suggest that the differences are perhaps too small to represent a reliable test to indicate an EVD-associated infection. Though the study sample size is small, and the study is underpowered to identify type I and type II errors, there is a concern that CSF parameters may not be reliable indicators (neither sensitive nor specific) of infection, i.e., CSF cell counts and indices remain unchanged despite clinically suspected and culture proven infection.

The recommendation, therefore, is that the decision to treat with antibiotics should depend on the clinical picture of each patient, and the results of the CSF Gram stain or cultures rather than other indices.

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The authors have provided a retrospective analysis of patients in two medical centers with extraventricular drains (EVD) that became infected. They address the question of whether there are reliable measures to make the diagnosis of EVD infection prior to positive CSF Gram stain or culture results, thereby allowing earlier therapy.

Unfortunately, the routine sampling of CSF parameters was not predictive of subsequent infection due to the confounding inflammatory effects of intraventricular blood in this patient population. Cytokine and other biomarkers in the CSF may allow for an earlier diagnosis of infection but are as yet unproven. At present, clinical assessment of the patient in light of his laboratory studies provides the indication for starting empiric antibiotic therapy prior to culture reports.

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