Title: Modalities and accuracy of diagnosis of external ventricular drainage—related infections: a prospective multicentre observational cohort study

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We would like to disclosure that partial results of this study were presented as conference poster entitled "Does antibiotic prophylaxis influence the incidence of EVD-related infections? A prospective multicentre study" at the 30th Annual Congress of the European Society of Intensive Care Medicine (ESICM), held in Vienna on the 23 - 27 September 2017.

Abbreviations and acronyms:

AB: Antibiotic; AUC: Area under the curve; AUROC: AUC area under the ROC curve; CD-ERI: clinically diagnosed EVD related infection, CP-ERI: culture-proven EVD related infection, CSF WBCC: CSF white blood cell count; CNS: central nervous system; CoNS: Coagulase-Negative Staphylococci; CRP: C-reactive protein; CSF: cerebrospinal fluid; ERI: EVD-related infection; EVD: external ventricular drain; GCS: Glasgow Coma Score; GOS: Glasgow Outcome Score; ICH: intracerebral haemorrhage; ICP: intracerebral pressure; ICU: intensive care unit; LOS: length of hospital stay; PMN: Polymorphonuclear Neutrophils; RBC: red blood cell; RBCC: red blood cell count; ROC: Receiver operating characteristic; S-CRP: serum C-reactive protein; S-WBCC: Serum white blood cell count; SAH: subarachnoid haemorrhage; SIRS: systemic inflammatory response syndrome; TBI: Traumatic brain injury; WBC: White Blood Cell

Abstract:

Background: Device infection is a major complication of placement external ventricular drains (EVD). Diagnostic features are often masked by underlying disease or cerebrospinal fluid (CSF) contamination by blood. We aim to assess which diagnostic modalities are applied for EVD-related infection (ERI) diagnosis and evaluate their accuracy.

Methods: This observational prospective study included 187 adult patients with an EVD. Modalities of clinical diagnosis of ERI diagnosed by treating physicians on clinical grounds and blood and CSF analysis (CD-ERI) were assessed prospectively. Additionally, the diagnostic accuracy of clinical and laboratory parameters for the diagnosis of culture proven ERI (CP-ERI) was evaluated, using data of the study patients and including a retrospective cohort of 39 patients with culture-proven ERI (CP-ERI).

Results: Thirty-one CD-ERIs were diagnosed in the prospective cohort. Most physicians used CSF analysis to establish the diagnosis. ROC analysis revealed an AUC of 0.575 (p=0.0047) for the number of positive SIRS criteria and AUC of 0.5420 (p= 0.11) for the number of pathological neurological signs for diagnosis of CP-ERI. Diagnostic accuracy of laboratory values was AUC 0.596 (p=0.0006) for serum white blood cell count (WBCC), AUC 0.550 (p=0.2489) for serum CRP, AUC 0.644 (p< 0.0001) for CSF WBCC and AUC 0.690 for CSF WBC/red blood cell count ratio (both p< 0.0001). Neither a temporal trend in potential predictors of CP-ERI nor a correlation between clinical diagnosis and proven CSF infection was found.

Conclusions: Clinicians base their diagnosis of ERI mostly on CSF analysis and occurrence of fever, leading to over-diagnosis. The accuracy of the clinical diagnosis is low. Commonly used clinical and laboratory diagnostic criteria have a low sensitivity and specificity for ERI.

Key words: External Ventricular Device, EVD-related infection, diagnosis, CSF changes

Introduction:

The insertion of an external ventricular drain (EVD) is a common and potentially lifesaving procedure in neurocritical care[9]. EVDs are often used for monitoring of intracerebral pressure (ICP) and drainage of cerebrospinal fluid (CSF) in the context of intracerebral haemorrhage (ICH), subarachnoid haemorrhage (SAH) and traumatic brain injury (TBI)[2,37]. EVD-related Infection (ERI) is one of the major complications of EVD placement, representing a serious hospital-acquired infection. Reported incidences of EVD-related infections range from 5% to more than 20% of EVD-placements [1,4,8,18,38,2,10,15,23,25,27] and are associated with poorer neurological outcomes, increased healthcare costs and prolonged hospital stays [16,10,15,23-25,27].

Rapidly available parameters for the diagnosis of ERI include clinical signs such as fever, nuchal rigidity and a change in mental status, blood tests including elevated white blood cell (WBC) count, neutrophilia with a shift towards immature band forms or elevated serum C - reactive protein (CRP)[3] and altered CSF parameters – such as increases in CSF white blood cell count (CSF WBCC). However, clinical features of EVD-related central nervous system infection are often masked by an altered level of consciousness due to the patient´s underlying condition or because of the frequent use of sedation in neuro-critical care patients. 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. Finally, changes in CSF parameters can be concealed by the presence of blood in the CSF space common in ICH, SAH and TBI patients, making the diagnosis of ERI difficult[34,7].

Positive CSF Gram stains and/or cultures in the context of new clinical signs of CNS infection plus changes in CSF parameters represent the gold standard for the diagnosis of an EVD-related infection.[35,19] However, Gram stains often are negative even in culture-positive CSF[31] and CSF cultures take several days until bacterial growth can safely be excluded and do not allow early diagnosis of infection. Therefore only in a minority of patients a certain diagnosis of culture proven ERI (CP-ERI) can be made based on evidence for the presence of bacteria in the cerebrospinal space. Most often clinicians have to base diagnosis and treatment on clinical features in correlation with changes in blood and CSF parameters (clinically diagnosed ERI [CD-ERI]).

Recommendations for diagnosis and treatment of ERI represent expert opinion and are deducted from established criteria for the diagnosis of non-EVD-related central nervous

system (CNS) infections [34,2,28,35,6,12]. Information on which parameters clinicians base the diagnosis of EVD-infections is not reported in the literature.

In this study, we aim to prospectively assess which diagnostic modalities to detect ERI are most commonly applied by clinicians in the neurocritical care setting. Additionally, we evaluate the diagnostic accuracy of these parameters in a large cohort of patients.

Methods and Materials:

Study design: Prospective observational multicentre study with a *post hoc* analysis that includes a retrospective cohort for comparison.

Setting: Patients were enrolled in the intensive care units (ICU) of the University Hospital of Bern, Switzerland (centre 1), Royal North Shore Hospital of Sydney (centre 2) and the Alfred Hospital in Melbourne (centre 3), Australia.

Participants:

- *Prospective Cohort*

Consecutive patients over 16 years of age suffering from ICH, SAH or TBI in whom an EVD was inserted during the study period of 24 months were enrolled in the study (prospective period). Patients with diagnosed or suspected primary CNS or systemic infection [34] and patients receiving systemic antibiotic treatment in the 72 hours before EVD placement were excluded.

- *Retrospective cohort*

Because of a very low number of positive CSF cultures and Gram stains in the prospective cohort, we included a second, retrospective cohort of patients from centre 1 and 2 with proven ERI. Records of all adult patients older than 16 years of age suffering from ICH, SAH or TBI in whom an EVD was inserted over a period of five years prior to study commencement were reviewed. Patients with diagnosed or suspected primary CNS or systemic infection [34] and patients receiving systemic antibiotic treatment in the 72 hours before EVD placement were not included in the retrospective cohort.

Data sources: Collected baseline characteristics in both cohorts included patient demographics, main diagnosis, Glasgow Coma Score (GCS), Hunt & Hess[21]and Fisher[11] grading systems for SAH and ICH score[17] for ICH at ICU admission, length of hospital stay (LOS), survival at hospital discharge and Glasgow Outcome Score (GOS). Clinical data included 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). In the case of

sedated patients where conclusive assessment of neurological status was not possible, signs of CNS infection were rated as absent. Laboratory data included all available measurements of red blood count (RBCC), serum WBCC count, serum C-reactive protein (CRP) level, CSF RBCC, CSF WBCC, CSF Gram stain and CSF cultures. Blood tests were performed on a daily or alternate-day basis and CSF samples were regularly (every 24 to 72h) collected from the day of EVD placement as per routine care. For data collection and statistical analysis, the day of EVD insertion was defined as day 0. Patient records were matched with the microbiology database of all cultured microorganisms in CSF and all positive Gram stains of CSF to identify patients with proven EVD-related infections during the course of the hospital stay. In the prospective cohort, the experience level of the person placing the EVD and aspects of surgical technique, the type of antibiotic strategy used, and the duration of catheter use were also collected.

Diagnosis of ERI: In the prospective cohort, the treating clinicians had to fill out a questionnaire to report occurrence of CD-ERI or non-EVD related infections and subsequent antibiotic treatment. Physicians were required to indicate on which of the following parameters the diagnosis suspicion had been based: serum WBCC, percentage of blood WBC band forms, serum CRP levels, CSF cell count, CSF RBCC/WBCC ratio, presence of positive SIRS criteria and/or clinical signs of CNS infection.

In both cohorts, CP-ERI was defined as occurrence of a positive CSF culture or Gram stain and concomitant occurrence of at least two SIRS criteria (temperature >38.3 °C or <36 °C, heart rate >90 beats/min, respiratory rate >20 breaths/min or $PaCO_2$ < 32 mmHg) or occurrence of one of any neurological sign of CNS infection (nuchal rigidity, headache, or changes in mental status) plus increased CSF WBCC[34].

Statistical analysis: Data is presented as mean and standard deviation or median and quartiles as indicated. Normal distribution was established using D'Agostino & Pearson omnibus normality test.

Fisher´s Test, *Chi*-square, student´s *t*-test and Mann-Whitney *U* test were used to compare variables of patients with and without CD-ERI in the prospective cohort of study patients. Chi Square test was used to detect a significant correlation between the clinical diagnosis of ERI

and CP-ERI in the prospective group.

The correlation between clinical signs, blood results or CSF parameters and occurrence of CP-ERI was assessed using data from both, the prospective and retrospective cohort combined. Patient-days were classified according to their temporal relation to the time point of diagnosis of CP-ERI as pre-infection, peri-infection (within 48h before and after diagnosis of CP-ERI) and post-infection (>48h after diagnosis of CP-ERI). Data from pre-infection patient days versus peri-infection patient days were used to evaluate the predictive value of clinical and laboratory indicators in predicting CP-ERI. Receiver operating characteristic (ROC) curves were constructed plotting sensitivity vs. 1-specificity to evaluate the predictive value of clinical and laboratory indicators in predicting occurrence of culture positive ERI; the results are reported as area under the ROC curve (AUROC) and significance value.

Additionally, linear mixed-effect models were used to assess temporal changes of parameters potentially indicating ERI and differences between patients with and without CP-ERI. Results are reported as F value and significance p. Potential temporal curve changes based on a 7-day time period before the development of diagnosed infection were assessed by fitting growth curves up to a third order polynominal as a covariate and occurrence of infection as fixed effect. In patients in which no CP-ERI occurred, the first 7 days after EVD insertion was used as comparison period. Statistical significance was determined when $p<0,05$ (two-sided). All statistical analyses were performed using IBM SPSS Statistics 24 (SPSS Inc. Chicago, Illinois).

Ethics approval: The study protocol was reviewed and approved by the relevant institutional review boards (Ethics Committee Bern, Switzerland; the Alfred Health Ethics Committee, Melbourne, Australia; and the Hawkesbury Human Research Ethics Committee, Northern Sydney Central Coast Health, Australia). All procedures were in accordance with the institutional and national research committees and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Results:

The baseline characteristics of both cohorts, the number of culture or gram stain positive ERIs and causal organisms are presented in Table 1.

Clinical diagnosis of EVD-related infection in the prospective cohort:

Thirty-one CD-ERIs occurred. The main diagnostic parameters on which ERI was based and technical aspects of EVD placement and are presented in Table 2, in groups stratified by presence/absence of clinical EVD infection. There was no significant difference in age and LOS for the presence of CD-ERI. There was no significant correlation of age and LOS and occurrence of CD-ERI. One hundred and forty-two non-EVD related infections were diagnosed. Pneumonia was the main other form of infection (78 patients, 54.9%), followed by bloodstream infection (7 patients, 4.7%). Infections not related to EVD placement had an onset time of 5.3±4.8 days, while CD-ERIs developed later, although without significant difference (p=0.134). In 25.4% of EVD-days systemic antibiotics were used, either for prophylaxis or treatment of CD-ERI or for treatment of other infections. Most patients received antimicrobial treatment with 3rd or 4th generation cephalosporins, according to local protocol.

Most physicians used CSF analysis to establish presence of CD-ERI, with CSF WBCC the most relevant criterion. A combination of more than one criterion was used in 16 cases (45,7%). Neurological signs of nuchal rigidity and altered consciousness, as well as positive CSF cultures and CSF changes (elevated CSF protein, elevated CSF lactate and reduced CSF to blood glucose ratio) were not used as a diagnostic criteria by any physicians. Single-shot antibiotic prophylaxis for EVD placement was used in 125 patients (66.8%), whereas 62 patients (33.2%) received continuous prophylactic antibiotics for the duration of EVD drainage. Antimicrobial empirical treatment choices are summarized in Table 2. There were 414 antibiotic-exposure days. All patients but one received systemic antimicrobial treatment; none of them were treated with intraventricular antibiotics and none of the EVDs was antibiotic-coated. Monotherapy was only used in 7 patients (20%). Most frequently, antimicrobial combinations included dual therapy with glycopeptide plus carbapenem (20%) and triple therapy with cephalosporin plus metronidazol plus glycopeptide (20%).

One hundred and sixteen EVD days were counted in the prospective cohort. Episodes of

abnormal temperature occurred 503 times (31.1% of EVD days), increased *heart rate* and *respiratory rate* were present in 690 (42.7%) and 624 (38.6%) episodes, respectively. Incidence for signs and symptoms of central nervous system infection was: 21 episodes (1.3%) of *nuchal rigidity;* 150 episodes (9.3%) of *decreased mental status;* and 187 episodes (11.6%) of *headache.* A total of 553 episodes (34.2%) of two or more positive SIRS criteria occurred. The range and incidence of pathological results of potential indicators of ERI are summarized in Table 3. Finally, the Chi Square test did not reveal a significant correlation between the clinical diagnosis of ERI and proven CSF infection in the prospective cohort (p=0.0580).

Prediction of CP-ERI using clinical features and blood and CSF parameters using both cohorts: A total of 46 CP-ERI occurred in the two study cohorts (7 in the prospective and 39 in the retrospective cohort). The CP-ERI rate was 4.33 cases per 1000 catheter-days in the prospective cohort. The ROC analysis of potential clinical indicators of EVD infection revealed an AUROC of 0.575 (95%-CI 0.5194 - 0.6307, p= 0.0047) for the number of positive SIRS criteria, and an AUROC 0.5420 (95%-CI 0.4880 - 0.5960, p= 0.11) for the number of pathological neurological signs. Figure 1 shows the results of the ROC analysis of laboratory data potentially indicating EVD-related infections. S-WBCC, CSF WBCC and CSF RBCC/WBCC ratio revealed an AUC of significantly >0.5. Table 4 reports the temporal trends of single potential predictors of ERI in groups stratified by the presence/absence of proven ERI. No significant temporal trend in potential predictors of CP-ERI was found during the 7 days prior to culture or gram stain proven ERI, indicating that no significant increase in number of SIRS criteria and neurological signs of CNS infection occurred nor higher levels of S-CRP or increases in S-WBCC, CSF WBCC and CSF WBCC/RBCC ratio were measured in the lead up to CP_ERI Patients *without* CP-ERI showed significant changes of SIRS criteria and S-CRP over time during the first 7 days after EVD placement.

Discussion:

In our multicentre observational study, clinicians based their diagnosis of ERI mostly on CSF analysis and the occurrence of fever. The frequency of CD-ERI was considerably higher than the incidence of CP-ERI and the two were not correlated. Our analysis indicates that commonly used diagnostic parameters have a low sensitivity and specificity for detection of ERI.

There are several limitations to our study. Because of the low number of CP-ERI in our prospective sample, we needed to use a retrospective cohort. This may introduce heterogeneity in the study population and entails the use of a more complex methodology and statistical analysis. In order to minimize this bias, we identified the retrospective cohort using the same inclusion and exclusion criteria and baseline characteristics as for our prospective group. Additionally, the parameters used in the study analysis consist of laboratory values, defined measurements of vital signs included in the SIRS criteria and signs of CNS infection which are all routinely and prospectively assessed in all neuro-critical care patients. It can be assumed that these parameters are measured with the same precision in the prospective and retrospective cohort. Another important limitation was that data were restricted to parameters collected in the clinical context. This resulted in missing values and did not include more recently established infection markers, such as sTREM-1[13], for determining ERI. We used positive CSF culture or gram stain results as the gold standard diagnosis of ERI, but this might be associated with a bias caused by the suboptimal sensitivity and specificity of CSF gram stains and cultures for diagnosing EVD-related infection. Culture results can be impaired by concomitant antibiotic treatment, that was present in our patient cohort, during 25% of EVD-days (either for prophylaxis of ERI, treatment of ERI or treatment of concomitant infection). Nevertheless, we believe that our analysis is valuable and has several strengths: on the one hand, the trial included a large cohort of patients with EVDs; on the other hand, the focus of the study was on evaluating how the diagnosis of ERIs established in the context of current guidelines [34,19,12], which are mostly based on expert opinion, therefore justifying the need for a further analysis.

Timely diagnosis and the commencement of adequate antimicrobial therapy is key in improving patients' outcomes in ERIs and prompts clinicians to start empiric antibiotic

therapy in patients in whom ERI is suspected. Several authors [19,8,29] argue that only positive CSF cultures, in conjunction with CSF pleocytosis, low glucose level, or high protein level, reliably indicate EVD-related infection. In the absence of positive cultures, some researchers accept CSF pleocytosis alone as sufficient evidence of CSF infections [32,22]. However, other authors report that determining ERI based on CSF direct examination has been shown to have low sensitivity[35,36] and that CSF culture results are not readily available and not reliable. Our results indicate that clinicians base their diagnosis of EVD infection mainly on the presence of fever and increased CSF WBC counts. But such a diagnosis based on clinical and CSF criteria may be misleading: firstly, in the neurocritical population, SIRS criteria and pathological neurological findings can be a manifestation of the underlying disease or be influenced by concomitant treatment, such as sedation. Secondly, any type of systemic infection induces systemic inflammation and can lead to increased levels of CRP and serum WBCC and concurrent infections occur frequently. Finally, the presence of intraventricular blood can distort the typical CSF WBC/RBC ratio and be a non-infectious source of fever.

In our data, the number of positive SIRS criteria was significantly higher after the occurrence of proven infection, whereas the number of pathological neurological signs did not differ. The perceived lack of specificity for CD-ERI might explain why these clinical and laboratory indicators of infection were used less frequently for diagnosis of ERI.

Although retrospective data[13,14,37,30,5] have suggested that CSF WBCC and CSF WBCC/RBCC ratio are useful in the diagnosis of EVD-related infection, our analysis suggests that commonly used bedside clinical and laboratory parameters are not a reliable basis to diagnose or exclude ERIs. Occurrence of positive SIRS criteria and of neurological signs of infection did not sufficiently discriminate between states of confirmed or absent culture-proven EVD infection. We were not able to identify any cut-offs for serum or CSF parameters that were associated with acceptable sensitivity and specificity to be of value in the clinical context. Analysing serum or CSF levels of potential indicators of ERI over time – as opposed to using specific cut-off values – revealed a high inter-individual variability between measurements; and occurrence of CP-ERI was not associated with any significant temporal changes of diagnostic markers. Remarkably, only a third of the patients with proven ERI had

an elevated temperature. Typical neurological symptoms of ERI - such as headache, neck stiffness or decreased were only reported in 10% of patients. This might reflect the nature of device-associated infections, which are frequently caused by slow-replicating microorganisms of low virulence growing in biofilms, such as CoNS (Coagulase-Negative Staphylococci) and Propionibacterium acnes.

In accordance with other studies [7,26,37,8,28,2], the most common pathogens were CoNS. The spectrum of these microorganisms suggests that the patient´s skin flora is an important source of EVD infection. The type of antibiotic prophylaxis (periprocedural vs continuous) did not influence the incidence of EVD-related infections. In most patients receiving antimicrobial prophylaxis before EVD placement, the chosen regimes did not cover the cultured pathogen spectrum. The use of broad-spectrum penicillins and 2nd generation cephalosporins does not show adequate coverage of *Staphylococcus epidermidis[33]*, the main pathogenic agent of this group. Another important aspect is that the isolation of *S. epidermidis* and other CoNS in the CSF needs to be interpreted with caution, as this may represent contamination [20]. An analysis to explore if antibiotic treatment previous to EVD insertion protects against infection would be interesting and may have clinical consequences, but our data is very small for this exploratory analysis and we suggest it to be investigated with other studies.

Our study therefore raises the discussion that routine CSF analysis on a daily basis or at two day intervals is questionable, although it is the standard practice in most neuro-critical care units. CSF culture is the only diagnostic parameter with a high specificity, but its sensitivity impaired by antibiotic use so a restrictive antibiotic strategy for ERI and other infection could become a trend. We agree that if CSF infection is suspected, CSF cultures should be performed and empirical antibiotic treatment should be commenced, but treatment should be stopped immediately once cultures come back negative.

Because CSF parameters are difficult to interpret, others sources for laboratorial diagnosis should be sought. Promising other biomarkers of CSF infection already exist[13], but he specificity/sensitivity of these has not been assessed yet in patients treated with an EVD.

In conclusion, clinicians base their diagnosis of ERI mostly on CSF analysis and occurrence of

fever. The frequency of clinically diagnosed ERI is considerably higher than the incidence of proven ERI and the accuracy of the clinical diagnosis is low. This might lead to frequent use of antibiotic treatment, causing an increase in risk of inducing growth of antibiotic-resistant pathogens and impair the sensitivity of CSF cultures. Our analysis indicates that commonly used clinical and laboratory diagnostic criteria have a low sensitivity and specificity for detection of EVD-related infection, therefore routine analysis of CSF samples to screen patients for ERI does not seem to be justified.

Compliance with ethical standards

No funding was received for this research.

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.

Due to the observational nature of the study, which only used data obtained during routine care, formal consent is not required.

This article does not contain any studies with animals performed by any of the authors.

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Tables:

Table 1. Patient demographics, clinical characteristics and types of organisms grown in study subjects.

Variable	Patients enrolled in the Prospective Cohort n=187	Patients enrolled in the Retrospective Cohort n=39
Male, n (%)	102(54,5)	17(43,6)
Mean age (years)	53,65±17,99	48,4±16,9
Reason for EVD placement, n (%)		
ICH	48(25,7)	5(12,8)
SAH	85(45,5)	20(51,3)
TBI	54(28,9)	9(23,1))
Neurological findings at time of admission		
GCS (mean score ±SD)	8,83±4,15	9,4±4,7
Hunt & Hess Score (median)	3	3
Fisher Scale (median)	3	4
LOS (days)	24,8±25,7 (hospital)	16,6±11,9 (ICU)
Survival (at discharge)	141(75,4)	32(82,0)
Outcome (GOS) (median)	3	3
Number of positive CSF cultures	6	38
Number of positive CSF gram stains	1	18
Cultured Organism		
Staphylococcus aureus		4
Coagulase-negative staphylococci (CoNS)	3	14
Enterococcus faecalis		4
Enterobacteriaciae	2	8
Propionbacterium acnes	1	--
Pseudomonas aeruginosa		3
Acinetobacter spp		7
Sphingomonas paucimobilis		1
Bacillus		1

(CSF: Cerebrospinal Fluid, EVD: External Ventricular Drain, GCS: Glasgow Coma Score, GOS: Glasgow Outcome Score, ICH: Intracranial Haemorrhage, SAH: Subarachnoid Haemorrhage, TBI: Traumatic Brain Injury)

Table 2: EVD-placement characteristics and parameters for CD-ERI (prospective cohort)

Variable	Patients with occurrence of CD-ERI n=31	Patients without occurrence of CD-ERI n=156	P Value
Experience of doctor placing EVD			0,704
1 to 10 years	3(9,7%)	11(7,1%)	
11 to 25 years	11(35,5%)	67(42,9%)	
Over 25 years	17(54,8%)	78(50,0%)	
Location of EVD placement			0,242
Emergency Department	12(38,7%)	85(54,5%)	
ICU	1(3,2%)	6(3,8%)	
Operating Theatre	18(58,1%)	65(41,7%)	
Surgical Technique for EVD insertion			0,757
Long-tunnel	25(80,6%)	116(74,4%)	
Short-tunnel	4(12,9%)	26(16.7%)	
Straight	2(6,5%)	14(9,0%)	
Type of Site Shaving (Large Shaving/Small Shaving)	15(48,4%)/16(52,6%)	84(53,8%)/72(46,2%)	0.719
Number of attempts for placement (one/more than one)	24(77,4%)/7(22,6%)	133(85,3%)/23(14,7%)	0,413
Type of AB prophylaxis used (continuous/periprocedural)	13(41,9%)/18(58,1%)	49(31,4%)/107(68,6%)	0,353
Choice of diagnostic Parameters			
Positive CSF Stain	0,7%		
Elevated CSF WBC	22,5%		
Elevated CSF PMN	9,2%		
Elevated Serum CRP	2,8%		
Elevated Serum WBC	7,0%		
Fever	10,6%		
Choice of AB treatment			
Penicillin	7 (20%)		
Cephalosporin	17 (48,6%)		
Carbapenem	12 (34,2%)		
Glycopeptide	27 (77,1%)		
Metronidazol	10 (28,6%)		

(AB: Antibiotic, CD-ERI: clinically diagnosed EVD related infection, CSF: Cerebrospinal Fluid, CRP: C-Reactive Protein, EVD: External Ventricular Drain, ICU: Intensive Care Unit, PMN: Polymorphonuclear Neutrophils, WBC: White Blood Cells)

Table 3: Characteristics of different markers used in the diagnosis of CD-ERI (prospective cohort)

	Number of episodes	Min.	Max.	Mean	Std. Deviation	Pathological findings Number of episodes
Serum CRP (mg/L)	687	2	542	79.95	85.021	**> 10 mg/L:** 571 (83,1%)
Serum WBC (cells/ml)	1486	3	38100	5249.53	6317.624	**>12,000/mL:** 245 (16,5%)
Serum WBC immature bands (%)	198	0	62	18.56	14.443	
CSF RBC (cells/µL)	944	0	1590750	61738.21	150651.104	
CSF WBC (cells/µL)	915	1	4750	113.91	336.063	**≥5 cells/µL:** 643 (70,3%)
CSF PMN (cells/µL)	689	1	4350	102.22	303.873	
CSF Protein (mg/dL)	146	1	893	47.06	112.307	**>45 µg/dL:** 35 (24,0%)
CSF Lactate (mmol/L)	505	0	13	2.80	1.258	**>4 mmol/L:** 74 (4,6%)
CSF pH	199	7	9	8.01	.290	
CSF Glucose (mmol/L)	441	1	8	4.13	.961	
Serum Glucose (mmol/L)	1438	3	22	8.19	2.171	
CSF/Serum Glucose Ratio	398	.20	1.67	.5437	.15998	**<0.5:** 130 (32,7%)
CSF WBC/RBC Ratio	898	.00	1.00	.0181	.07046	**>0,01:** 229 (25,5%)

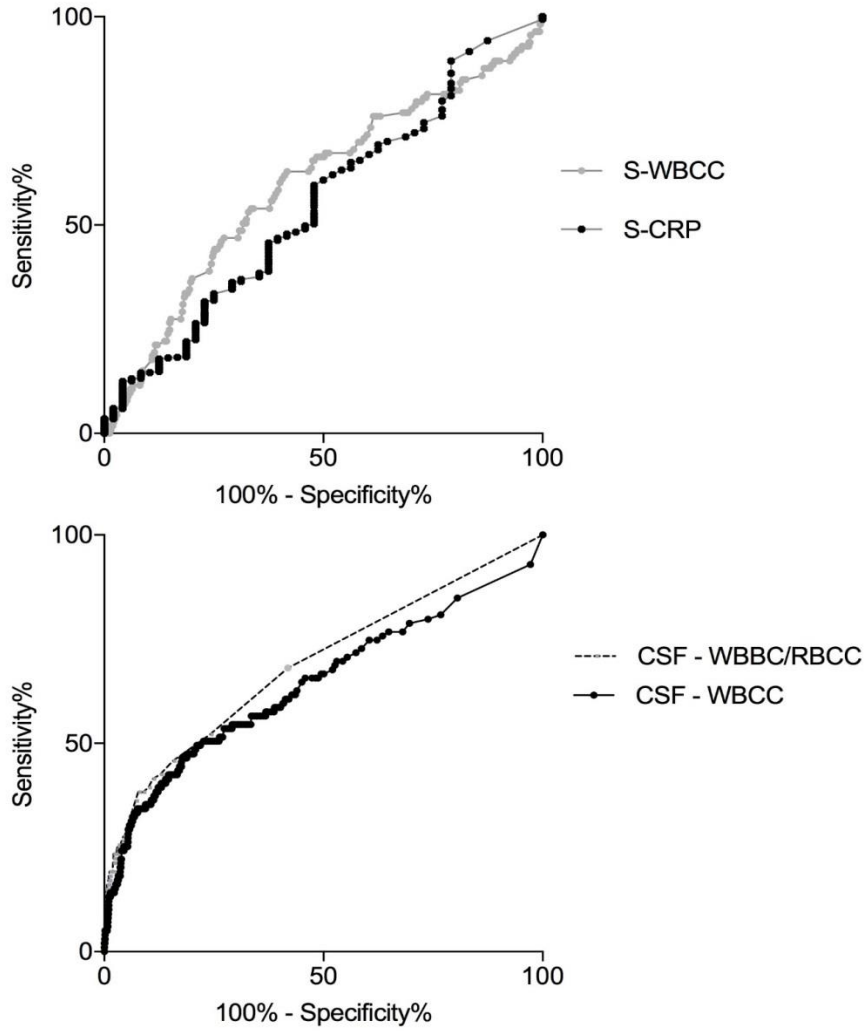
CD-ERI: clinically diagnosed EVD related infection, CSF: Cerebrospinal Fluid, CRP: C-Reactive Protein, PMN: Polymorphonuclear Neutrophils, RBC: Red Blood Cells, WBC: White Blood Cells)

Table 4: Analysis for temporal trends of single potential predictors of ERI in groups stratified by presence/absence of CP-ERI *(combined data from both cohorts*). The table describes if a linear, square and cubic increase in number or levels of parameters occurs in the lead up of CP-ERI or during the first 7 days after EVD placement (patients without occurrence of CP-ERI), model parameters are reported as weighing factor F and respective significance level.

		SIRS criteria		**Neurological signs**		**S-CRP**		**S-WBCC**		**CSF WBCC**		**CSF WBCC/RBCC ratio**	
		F	*p*	F	*p*	F	*p*	F	*p*	F	*p*	F	*p*
CP-ERI (n=180)	Time	3.112	0.079	0.237	0.627	0.227	0.634	0.061	0.805	0.002	0.960	0.113	0.737
	$Time^2$	3.767	0.053	0.000	0.995	0.085	0.772	0.049	0.825	0.038	0.846	0.200	0.655
	$Time^3$	2.783	0.096	0.004	0.952	0.178	0.674	0.002	0.967	0.220	0.639	0.016	0.901
No CP-ERI (n=46)	Time	5.205	**0.023**	0.082	0.775	21.355	**0.000**	0.459	0.498	0.459	0.498	1.444	0.230
	$Time^2$	2.219	0.137	0.949	0.330	5.724	**0.017**	0.299	0.584	0.299	0.584	1.454	0.228
	$Time^3$	1.475	0.225	1.460	0.227	1.407	0.236	0.162	0.688	0.162	0.688	1.531	0.216

(CP-ERI: culture-proven EVD related infection) CSF: Cerebrospinal Fluid, EVD: External Ventricular Drain, PMN: Polymorphonuclear Neutrophils, RBCC: Red Blood Cell Count, S-CRP: Serum C-Reactive Protein, SIRS: Systemic Inflammatory Response Syndrome, S-WBCC: Serum White Blood Cell Count)

Figure 1. ROC Curves for serum and CSF parameters used for diagnosis of ERI *(combined data from both cohorts).*



Legend 1: Illustration of the ROC curves for serum parameters [white blood cell count (S-WBCC) and serum C-reactive Protein (S-CRP)] (upper plot) and CSF parameters [CSF WBCC/RBCC Ratio and CSF white blood cell count (CSF WBCC)] (lower plot). S-WBCC: AUC 0.596 (95% CI 0.538 - 0.654); p=0.0006, S-CRP: AUC 0.550 (95% CI 0.465 - 0.634), p=0.2489; CSF WBCC/RBCC ratio: AUC 0.690 (95% CI 0.626 - 0.753), p< 0.0001; CSF WBCC: AUC 0.644 (95% CI 0.576 to 0.711), p< 0.0001.