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Diagnostic Accuracy of Clinical Signs and Biochemical Parameters for External Ventricular Cerebrospinal Fluid Catheter-Associated Infection

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ABSTRACT

Background and objectives: Few prospective well-designed diagnostic accuracy studies have been performed to study the parameters of infection in patients suspected for external ventricular catheter-associated infection. Our objective was to analyze the diagnostic accuracy of clinical characteristics and biochemical and

microbiological parameters in diagnosing external ventricular cerebrospinal fluid (CSF) catheter-associated infection.

Methods: From 2014 to 2017 we performed a single-center cohort study in consecutive patients at the intensive care unit who required an external ventricular CSF catheter in the Hague, the Netherlands. CSF was sampled and analyzed daily. Ventricular catheter-associated infection was defined according to the 2017 Infectious Diseases Society of America's Clinical Practice Guidelines. We compared clinical characteristics and biochemical parameters between patients with and without infection from 3 days prior to 3 days after the day the CSF sample was collected that grew bacteria.

Results: 103 patients were included of whom 15 developed a catheter-associated infection (15%). The median day cultures were positive was 3 days after CSF collection (IQR +2 to +4). On day 0, none of the tests could differentiate between patients with and without infection. CSF leukocyte count was increased in patients with ventricular catheter-associated infection as compared to patients without on day +2 and +3. The difference was most prominent on day +2 (1703 $x10^6$/L [IQR 480-6296] vs. 80 $x10^6$/L [IQR 27-251]; p<0.001; AUC 0.87 [CI 0.71-1.00]). Sensitivity for CSF leukocyte count at a cut off level >1000 $x10^6$/L was 67% (95% CI 30-93) and specificity was 100% (95% CI 90-100), the positive predictive value was 100% and the negative predictive value was 92% (95% CI 83-97). The percentage polymorphonuclear cells was higher in patients with infection on day +1 and +2 (day +2 89% [IQR 78-94] vs 59% [IQR 39-75]; p<0.01; AUC 0.91 [95% CI 0.81-1.0]).

Discussion: An elevated CSF leukocyte count and increased percentage polymorphonuclear cells are the strongest indicators for external catheter-associated infections on the days prior to culture positivity. New CSF markers of drain-associated infection should be studied to enable earlier diagnosis and treatment in patients with an infection, and reduce antibiotic treatment in those with no infection.

Classification of Evidence:

This study provides Class I evidence that in individuals requiring an external ventricular CSF catheter, elevated CSF leukocyte count and an increased percentage polymorphonuclear cells are the strongest indicators of catheter-associated infections in the days prior to CSF culture positivity

INTRODUCTION

There is a high rate of infection in patients with external ventricular catheters, which has been associated with increased duration of drainage, leakage of cerebrospinal fluid at the site, obstruction of the drain, routine CSF sampling, cranial fracture with CSF leak and intraventricular hemorrhage.[1-3] Making a diagnosis of external

catheter-associated infection can be difficult in patients on the intensive care unit, with decreased level of consciousness and severe illness.[3] Making a definite diagnosis requires positive CSF cultures, but this can take several days to become positive if they will be positive at all.[4] Guidelines therefore recommend to start antibiotic therapy on clinical suspicion.[2-3] If the results of CSF cultures subsequently remain negative, antibiotic treatment can be withdrawn after 72 hours, although treatment should be continued in those with high level of suspicion for infection even if cultures remain negative.[2] After a systematic review and meta-analysis we recently concluded that clinical factors and biochemical and microbiological measures have limited diagnostic value in differentiating between ventriculitis and sterile inflammation in patients with external CSF catheters.[4] Few prospective well-designed diagnostic accuracy studies have been performed to study the CSF parameters of infection to predict infection in patients suspected for catheter-associated infection.[2-4] With our research we aimed to answer the research question about the diagnostic accuracy of clinical characteristics and biochemical and microbiological parameters in diagnosing external ventricular cerebrospinal fluid (CSF) catheter-associated infection.

METHODS

Patient population

We performed a single-center observational cohort study including consecutive adult patients admitted to the Intensive Care Unit (ICU) of the Haaglanden Medical Center (a large non-academic teaching hospital) with external ventricular CSF catheters. Exclusion criteria were expected death within 24 hours and a central nervous system infection at presentation.

We prospectively gathered clinical characteristics including Glasgow Coma Scale (GCS) score and temperature daily from day of admission until discharge date. As part of the local standard operating procedures, CSF was analyzed daily for leukocyte count, glucose-, lactate- and protein concentration. For calculating the cell index, the following formula was used: the leucocyte to erythrocyte ratio in CSF divided by the leucocyte to erythrocyte ratio in blood.[5] If a patient received bilateral external ventricular catheters, we collected CSF from both drains simultaneously.

Blood samples were analyzed for leukocyte count, erythrocyte count, C-reactive protein, lactate and glucose concentration. Culture and Gram stain of CSF was performed daily. The collection of CSF and blood was continued until the drain was removed.

Insertion and maintenance of drains

External antibiotic impregnated ventricular catheters (Bactiseal®, Codman, Johnson & Johnson, Wokingham, UK) were inserted in an operating theatre under sterile conditions with subcutaneous tunneling for several centimeters. Perioperatively, 1000 mg of cefazolin was administered. A closed external drainage and monitoring system (Exacta; Medtronic, Inc., Minneapolis, MN) was connected to the catheter. The CSF samples were obtained from this closed system via a standard operating procedure at the proximal stopcock. To prevent differences in CSF composition due to diurnal changes CSF was always sampled in the morning (between 8-9 AM). As part of standard care all patients received Selective Oropharyngeal Decontamination (SOD) with tobramycin, colistin and amphotericine B, this was discontinued when a patient was transferred to the neurosurgery/neurology department.

Infection definition

Patients were retrospectively classified as having a catheter-associated infection according to the 2017 Infectious Diseases Society of America (IDSA) guidelines.[2] In this guideline, an infection is defined as *'single or multiple positive CSF cultures with CSF pleocytosis and/or hypoglycorrhachia, or an increasing cell count, and clinical symptoms suspicious for ventriculitis or meningitis*'. Patients with positive culture results secondary to contamination were categorized in the 'no infection' group. The IDSA-definition for contamination includes an isolated positive CSF culture or Gram stain, with normal CSF cell count and glucose and protein concentrations and no clinical symptoms suspicious for ventriculitis or meningitis.[2] As most patients had CSF abnormalities due to the primary neurological condition, e.g. increased leucocyte count due to a subarachnoid hemorrhage, we deemed this definition to be unsuitable. Therefore, contamination was defined as a positive culture result without the start of antibiotic treatment for catheter-associated infection by the treating physician and without subsequent clinical deterioration of the patient.

In culture proven catheter-associated infection, the day the first positive culture CSF sample was gathered was considered the first day of infection and was named 'day 0'. Timing of CSF collection days for controls was

matched to the number of days between drain placement and infection in patients with catheter-associated infection (median 9 days, samples analyzed from day 6-12 after placement).

Statistical analysis

Variables were expressed as mean with standard deviations (SD) or median with interquartile range (IQR). Group characteristics were compared between patients with and without infection by using a χ^2 test for nominal variables and Mann-Whitney U test for continuous variables. A p-value <0.05 was considered significant. We analyzed the predictive value of CSF parameters from three days prior to three days after the diagnosis by comparing values to day 0 and comparing them to the previous day by using the Wilcoxon signed rank test. We decided to analyze our data up to three days prior to day 0 to enable detection of an early infectious response. We performed the analysis up to three days after day 0 to analyze the diagnostic value of clinical factors and biochemical and microbiological measures up to the median number of days it takes for bacteria to be cultured [8]. We did not correct for missing data, nor did we impute missing data. Clinical and laboratory parameters were analyzed using SPSS version 26.

Bias

By including consecutive adult patients admitted to the ICU, selection bias was avoided. External catheter-associated infection was diagnosed by two investigators according to the IDSA guidelines. If there was a discrepancy in diagnosis, consensus was achieved by discussion.

Standard protocol approvals, registrations and patient consents

The local Medical Ethical Committee approved the study. The ethics board determined that participant consent was not required.

Data availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Classification of Evidence:

This study provides Class I evidence that in individuals requiring an external ventricular CSF catheter, elevated

CSF leukocyte count and an increased percentage polymorphonuclear cells are the strongest indicators of catheter-associated infections in the days prior to CSF culture positivity.

RESULTS

From August 2014 to September 2017, 120 patients received an external ventricular catheter. Seventeen patients were excluded as they presented with central nervous system infection (n=8), catheter was removed within 24 hours (n=2), died within 24 hours (n=3), had an obstructed catheter (n=1) or because of unknown reasons (n=3; figure e-1).

The median age of the 103 included patients in the analysis was 61 years (IQR 50-70) and 48 (47%) patients were female (Table 1). The admission diagnosis was subarachnoid hemorrhage in 53 (51%) and intraventricular- or intraparenchymal hemorrhage in 39 patients (38%). The median Glasgow Coma Scale score (GCS score) at admission was 10 (IQR 7-13). An external ventricular CSF catheter was inserted after a median of 0 days after admission (range 0-3 days). Nineteen patients (18%) received bilateral EVDs. Overall, 1190 CSF samples of 1495 days of drainage were available for analysis (80%); and 379 of 496 days between day -3 to +3 – with day 0 the culture positive sample taken (76%).

Fifteen patients (15%) fulfilled the definition of a culture proven catheter-associated infection (table e-1). The median time from the start of external drainage until developing a catheter-associated infection was 9 days (range 3-16 days). The median number of drainage days was longer in patients who developed a catheter-associated infection (13 vs 9 days, p=0.004, figure 1). Antibiotic treatment was initiated after a median of 1 day after the first positive culture CSF was sampled (range -1 to +2 days). Other infections were diagnosed between day -3 to +3 in 8 of 74 (11%) patients without catheter-associated infection who had a catheter in situ between day -3 to +3. Other infections consisted of pneumonia in 4 (50%) and urinary tract infection in 4 (50%).

Microbiology results

CSF cultures were positive in 92 of 1158 cultures (8%). Of these, only 52 positive results (56%) in 15 patients were defined as infectious, while the other 40 were judged as contamination by the treating physician. The 52 CSF cultures were positive after a median time of 3 days (IQR 2-4 days, range 1-8 days) after sampling. CSF Gram stain showed bacteria in 20 of 52 culture positive CSF samples (38%) and in 8 of 15 patients (53%). CSF cultures showed coagulase negative Staphylococci (n=6), *Enterococcus faecalis* (n=2), *Klebsiella pneumoniae*,

Serratia marcescens, *Moraxella catarrhalis* and *Staphylococcus aureus* (each in 1 patient). Multiple pathogens were found in three patients (described in table e-1). In total, 40 of 92 positive cultures (43%) in 29 patients were considered to be contamination. None of these 29 patients received antibiotic therapy for catheter-associated infection. CSF Gram stain was negative in all of these 29 patients. Catheter tips were cultured after removal in 33 patients, showing causative bacteria 7 of 15 patients with meningitis (47%).

Clinical characteristics

Scores on the Glasgow Coma Scale were comparable between patients with and without infection on day 0 (table e-2). Body temperature was higher in patients with infection as compared to patients without infection on day +1 (. table e-3). On day +2, a higher proportion of patients with infection had fever (defined as more than 38.0°C) as compared to those without infection (11 of 13 [85%] vs. 21 of 39 patients [56%]; (sensitivity 85% [95%CI 55-98%], specificity 46% [CI 30-63%]; p=0.05, table 2).

CSF parameters

There were no differences in CSF parameters between patients with and without infection on the days prior to, and the day of, sampling of the first positive CSF culture (Day -3 to 0; table e-2, figures 2 and 3). CSF leukocyte count was increased in patients with external ventricular catheter-associated infection as compared to patients without on day +2 and +3 (table 2 and table e-4). The difference in CSF leukocyte count between patients with and without infection was most prominent on day +2 (1703 $x10^6$/L [IQR 480-6296] vs. 80 $x10^6$/L [IQR 27-251]; p<0.01; AUC 0.87 [95%CI 0.71-1.00]). The cell index was increased in patients with infection on day one, two and three (day +2 21.3 [IQR 7.0-114.9] vs. 0.9 [IQR 0.5-4.6]; p<0.01; AUC 0.93 [95% CI 0.85-1.0]) (table 2 and table e-3,e-4).

The glucose concentration in CSF and CSF to blood glucose ratio was lower in patients with ventricular catheter-associated infection on day +3 (table e-4). The percentage polymorphonuclear cells (PMNs) was higher in patients with infection on day +1 and +2 (table 2 and. table e-3). The difference was most prominent on day +2 (89% [IQR 78-94] vs 59% [IQR 39-75]; p<0.01; AUC 0.91 [0.81-1.0]. The CSF lactate concentration was comparable between patients with and without external catheter-associated infection on all seven days analyzed. The CSF to blood lactate ratio was higher in patients with catheter-associated infection on day +2 (table 2).

The total protein concentration was elevated in patients with catheter-associated infection on day +2 and +3 (table 2 and table e-4). At a cut off value of ≥0.6 g/L, on day +2 sensitivity was 70% (95% CI 35-93); specificity 72% (95% CI 55-86); PPV 41% (95% CI 26-58); NPV 90% (95% CI 77-96). Day +3 sensitivity was 78% (95% CI 40-97); specificity 72% (95% CI 53-86); PPV 44% (95% CI 29-60); NPV 92% (95% CI 77-98).

Systemic markers of infection

The leukocyte count and C-reactive protein in blood did not differ between patients with and without external ventricular catheter-associated infection on all days.

Course of CSF measures over time

In patients with infection, few significant changes in laboratory measures were observed when results were compared to previous days. There was a 4-5-fold increase in median CSF leucocyte count on day +1 as compared to day 0 (529 $x10^6$/L [IQR 33-7430] vs 129 $x10^6$/L [IQR 42-1174]; p=0.05). This increase was also observed when the CSF leukocyte count was corrected for blood admixture by using the cell index (day +1 7.2 [IQR 2.2-195.5] vs. day 0 0.98 [IQR 0.36-6.63]; p=0.03).

There was no difference in glucose concentration or -ratio over time except for the glucose concentration on day +2 which was lower as compared to day 0 (day +2 3.4 mmol/L [IQR 1.6-4] vs. day 0 4.2 mmol/L [IQR 3.6-5.2]; p=0.02). There was no significant change in CSF lactate concentrations or protein concentrations over days in patients with infection.

DISCUSSION

Our study shows that most clinical characteristics and laboratory parameters do not differentiate between patients with and without external ventricular CSF catheter-associated infection. An elevated CSF leukocyte count and increased percentage polymorphonuclear cells were the strongest indicators for external catheter-associated infections on the days prior to culture positivity with AUCs of 0.85 and 0.91 respectively. In our previously published meta-analysis, it was also shown that the leukocyte count in CSF was the most reliable indicator for catheter-associated infection.[4] However, the sensitivity of CSF leukocyte count was found to be suboptimal to rule out drain-associated infection at different cut-offs. This was mainly due to blood admixture secondary to the primary neurological condition and a sterile inflammatory response.[6] Correction for blood admixture by using the cell index provided only limited incremental value compared to uncorrected CSF

leukocyte count. In previously reported studies, the AUC of the cell index ranged from 0.63-0.83 which was comparable to the diagnostic accuracy of the non-corrected leukocyte count.[7-9]

We found that a positive Gram staining is diagnostic for external ventricular CSF catheter-associated infection with a positive predictive value of 100% and could be used to identify 8 of 15 infected patients (53%). However, false negative results occur frequently with a positive CSF Gram stain in only 38% of positive CSF cultures. These results are in line with the results of previously performed studies which reported a sensitivity of 45-50% and specificity of 100%.[10-11] Because of the high specificity, CSF Gram staining should be routinely performed in patients with suspected CSF drain related infections.

Because of the limited diagnostic value of clinical, blood and CSF examination in suspected external ventricular CSF catheter-associated infection there should be a low threshold for starting antibiotic treatment.[3] When there is a clinical suspicion of external ventricular CSF catheter-associated infection and CSF is send to the laboratory because of a suspected infections, antibiotic therapy should be initiated. Our results showed a median of three days before cultures grew bacteria with a range up to eight days. This is comparable to a previous study of 158 CSF samples, in which there was a mean duration of 3.0 days (SD 2.4 days, 95% CI 2.7-3.4 days; range 1-10 days) before cultures grew bacteria.[12] The British Society for Antimicrobial Chemotherapy advised to discontinue antibiotics when CSF cultures are negative after 72 hours.[13] This approach was shown to be effective and safe in a cohort of 75 post-neurosurgical patients with an elevated leukocyte count.[14] However, in the population of patients with external ventricular CSF catheter-associated infections, this approach seems inappropriate as we found that in 27% of patients, CSF cultures turn positive after this 72 hour time window. Therefore, antibiotic treatment should be continued irrespective of culture results after 72 hours if there is high clinical suspicion of infection.

Limitations

There are several limitations to our study. First, CSF was withdrawn daily as part of standard care. This daily withdrawal of CSF may have increased the risk of an infection by introducing bacteria during manipulation of the drain.[1,2] Previously, daily sampling of CSF was shown to increase the risk of infection in a retrospective cohort study (OR 1.08 [95% CI 1.01-1.17]).[15] In our cohort the rate of patients with infection (15%) was not higher than the 10-20% reported in previous literature, but given the pathogenesis of catheter-associated

infection, it is possible that, despite sterile drain-handling, the risk of developing a catheter-associated infection was increased.[1] Furthermore, the number of available CSF samples decreased after a ventricular catheter-associated infection was diagnosed. It is advised to remove the catheter as soon as catheter-associated infection is suspected, and therefore, the number of data were lower on day +3 as compared to day 0. Before removal of the drain, a drain challenge was performed. During the drain challenge no CSF was sampled, partially explaining the 20% missing data. Other data were missing at random. Nevertheless, our results provide a detailed insight in the dynamic of CSF parameters in patients with external ventricular CSF catheter-associated infections.

Our results demonstrate that the several clinical characteristics and laboratory parameters do not differentiate between patients with and without catheter-associated infection. A high CSF leukocyte count and high percentage polymorphonuclear cells are currently the strongest indicators for external catheter-associated infections. New CSF markers of drain-associated infection should be studied to enable earlier diagnosis and treatment in patients with an infection and reduce antibiotic treatment in those with no infection.

Take-home points:

- Most clinical characteristics and laboratory parameters do not differentiate between patients with and without external ventricular CSF catheter-associated infection.
- An elevated CSF leukocyte count and increased percentage polymorphonuclear cells are the strongest indicators for external catheter-associated infections on the days prior to culture positivity.
- Positive Gram staining is diagnostic for external ventricular CSF catheter-associated infection. False negative results frequently occur.
- There is no incremental value of daily CSF sampling.
- New CSF markers of drain-associated infection should be studied to enable earlier diagnosis and treatment in patients with an infection, and reduce antibiotic treatment in those with no infection.

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REFERENCES

1. Jamjoom AAB, Joannides AJ, Poon MT, et al. Prospective, multicentre study of external ventricular drainage-related infections in the UK and Ireland. J Neurol Neurosurg Psychiatry. 2018;89:120-126; doi: 10.1136/jnnp-2017-316415.
2. Tunkel AR, Hasbun R, Bhimraj A, et al. 2017 Infectious Diseases Society of America's Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis. Clin Infect Dis 2017;64: 701-706; doi: 10.1093/cid/ciw861.
3. van de Beek D, Drake JM, Tunkel AR. Nosocomial Bacterial Meningitis. N Engl J Med 2010;362:146-54; doi: 10.1056/NEJMra0804573.
4. Dorresteijn KRIS, Jellema K, van de Beek D, Brouwer MC. Factors and measures predicting external CSF drain-associated ventriculitis: A review and meta-analysis. Neurology 2019;93:964-972; doi: 10.1212/WNL.0000000000008552.
5. Pfausler B, Beer R, Engelhardt K, Kemmler G, Mohsenipour I, Schmutzhard E. Cell index - A new parameter for the early diagnosis of ventriculostomy (external ventricular drainage)-related ventriculitis in patients with intraventricular hemorrhage? Acta Neurochir (Wien). 2004;146:477–481; doi: 10.1007/s00701-004-0258-8.
6. Fam MD, Zeineddine HA, Eliyas JK, et al. CSF inflammatory response after intraventricular hemorrhage, Neurology 2017;89:1553-1560; doi: 10.1212/WNL.0000000000004493.
7. Liew S, Richards S, Ming Ho K, Murray R. Utility of the cell index in predicting external ventricular drain-related ventriculo-meningitis. Neurocrit Care, 2020 Dec;33(3)776-784; doi: 10.1007/s12028-020-00964-w.
8. Boeer K, Siegmund R, Pfister W, Isenmann S, Deufel T. Correction of ventricular cerebrospinal fluid (CSF) samples for blood content does not increase sensitivity and specificity for the detection of CSF infection. Clin Chem Lab Med 2008;46:842-848; doi: 10.1515/CCLM.2008.167.
9. Montes K, Jenkinson H, Habib OB, Esquenazi Y, Hasbun R. Corrected WBC count, cell index, and validation of a clinical model for the diagnosis of health care-associated ventriculitis and meningitis in adults with intracranial hemorrhage. Clin neurol neurosurg. 2019; 178: 36-41; doi: 10.1016/j.clineuro.2019.01.012.
10. Muttaiyah S, Ritchie S, Upton A, Roberts S. Clinical parameters do not predict infection in patients with external ventricular drains: A retrospective observational study of daily cerebrospinal fluid analysis. J Med Microbiol. 2008;57:207–209; doi: 10.1099/jmm.0.47518-0.
11. Wiegand J, Hickson L, Merz TM. Indicators of external ventricular drainage-related infections- a

retrospective observational study. Acta Neurochir (Wien) 2016;158:595-601; doi: 10.1007/s00701-016-2709-4.

12. Desai A, Lollis SS, Missios S, et al. How long should cerebrospinal fluid cultures be held to detect shunt infections? J Neurosurg Pediatr. 2009;4(2):184-9; doi: 10.3171/2009.4.PEDS08279.

13. Brown EM, de Louvois J, Bayston R, Lees PD, Pople IK. The management of neurosurgical patients with postoperative bacterial or aseptic meningitis or external ventricular drain-associated ventriculitis. Published online Jul 6, 2009. Accessed June 19, 2021. https://www.tandfonline.com/doi/abs/10.1080/02688690042834.

14. Zarrouk V, Vassor I, Bert F, et al. Evaluation of the management of postoperative aseptic meningitis. Clin Infect Dis. 2007;44(12):1555-9; doi: 10.1086/518169.

15. Williamson RA, Phillips-Bute BG, McDonagh DL. Predictors of extraventricular drain-associated bacterial ventriculitis. J Crit Care. 2014; 29 (1):77–82; doi: 10.1016/j.jcrc.2013.08.012.

TABLES

Table 1: Patient characteristics

Characteristics*	All patients (n=103)	Culture proven infection (n=15)	No infection (n=88)	P-value
Sex, female	48/103 (47)	8/15 (53)	40/88 (45)	0.57
Age	61 (50-70)	63 (47-69)	60 (51-70)	0.96
Immunocompromised**	6/103 (6)	1/15 (7)	4/88 (5)	0.55
GCS at admission	10 (7-13)	10 (7-14)	10 (7-13)	0.41
Indication for drain placement				0.8
Subarachnoid hemorrhage	53/103 (51)	6/15 (40)	47/88 (53)	
Intraventricular- or intraparenchymal hemorrhage	39/103 (38)	8/15 (53)	31/88 (35)	
Brain tumor	2/103 (2)	0	2/88 (2)	
Peri- and postoperative prophylactic drainage	4/103 (4)	1/15 (7)	3/88 (3)	
Other	5/103 (5)	0	5/88 (6)	
Drainage days	10 (5-14)	13 (11-18)	9 (5-14)	0.004
Death	23/103 (22)	5/15 (33)	18/88 (20)	0.32

*n/N (%) or median (IQR)

**** Medical history of currently active cancer (n=2) or the use of corticosteroids (n=3).**

Table 2: Clinical and biochemical characteristics present in patients with and without external ventricular catheter-associated infection - day 2.

	Median patients with infection (IQR)	Median patients without infection* (IQR)	P-value	AUC (95% CI)	Cut off	Patients with infection n/N (%)	Patients without infection* n/N (%)	Sensitivity** % (95% CI)	Specificity % (95% CI)	P-value
Temperature (°C)	39 (38.2-39.7)	38.1 (37.5-38.8)	0.02	0.73 (0.55-0.91)	**≥ 38.0**	11/13 (85)	21/39 (54)	85 (55-98)	46 (30-63)	0.048
CSF leukocyte count (x10^6/L)	1703 (480-6296)	80 (27-251)	<0.01	0.87 (0.71-1.00)	**> 5**	9/9 (100)	32/36 (89)			0.569
					> 100	8/9 (89)	15/36 (42)	89 (52-100)	58 (41-74)	0.022
					>1000	6/9 (67)	0/36 (0)	67 (30-93)	100 (90-100)	<0.01
CSF lactate conc. (mmol/L)	3.6 (2.3-11)	3 (2-3.4)	0.26		**≥ 4**	2/8 (25)	5/32 (16)			0.611
Lactate ratio	3.8 (3.0-11.9)	2.6 (2.1-3.7)	0.02	0.77 (0.61-0.93)						
CSF glucose conc. (mmol/L)	3.4 (1.6-4)	4.0 (3.2-4.6)	0.09							
CSF to blood glucose ratio	0.4 (0.02-0.6)	0.6 (0.5-0.6)	0.25		**< 0.6**	4/6 (67)	17/24 (71)			>0.99
					< 0.4	3/6 (50)	3/24 (13)			0.075
CSF total protein conc. (g/L)	0.99 (0.5-1.8)	0.48 (0.3-0.65)	0.01	0.75 (0.56-0.95)	**≥0.6**	7/10 (70)	10/36 (28)	70 (35-93)	72 (55-86)	0.025
Percentage PMN	89 (78-94)	59 (39-75)	<0.01	0.91(0.81-1.00)						
Cell index	21.3 (7.0-114.9)	0.9 (0.5-4.6)	<0.01	0.93 (0.85-1.00)						

*Patients we**re only included if the drain is in situ on day 11**

****Calculated in case a significant difference between patients with and without external ventricular catheter-associated infection was found**

Figures

Figure 1: Infection occurrence over days.

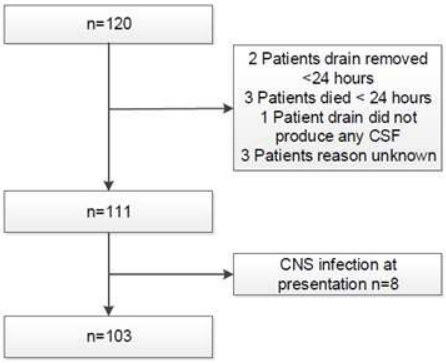


Figure 2: CSF measures over time (leukocyte count, % polymorphonuclear cells, protein concentration and cell index).

Median results and IQR for leukocyte count in CSF (A), percentage polymorphonuclear cells (B), total protein concentration in CSF (C), cell index (D) on the three days before infection and the first three days of infection. Significant differences are indicated with '*'.

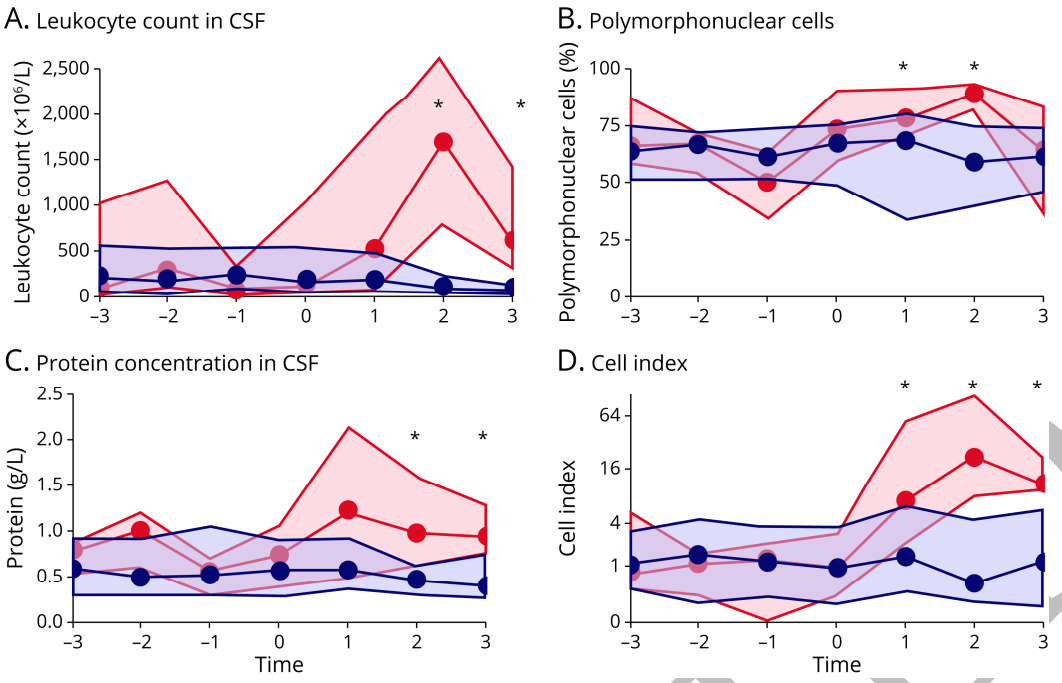
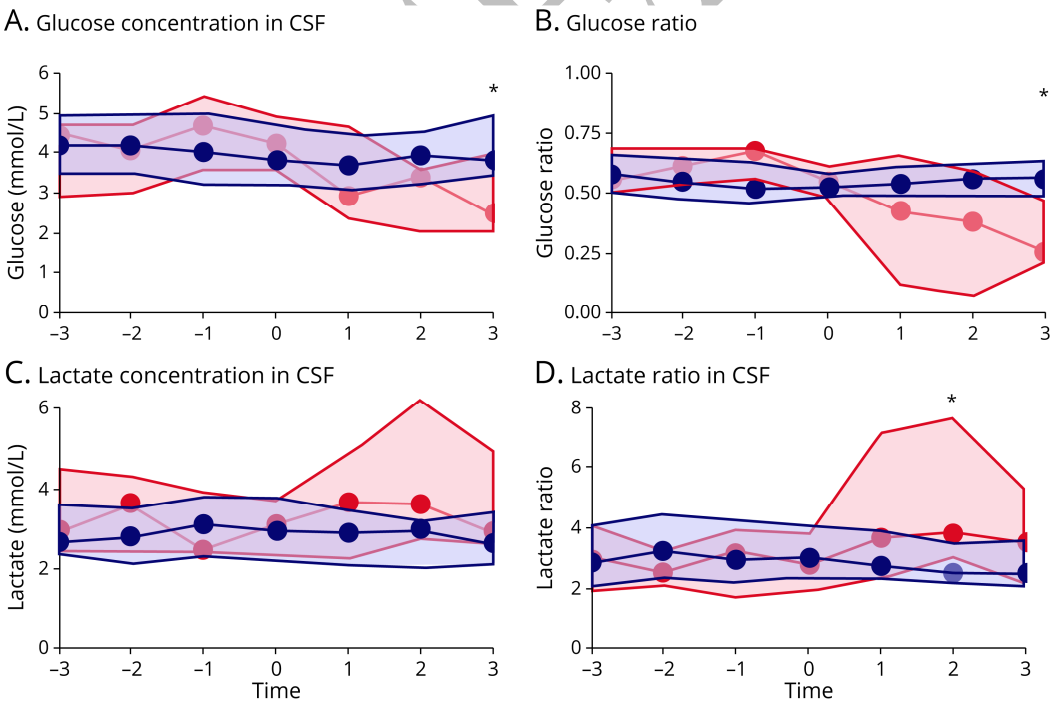


Figure 3: CSF measures over time (glucose concentration and CSF/blood ratio, lactate concentration and -ratio) Median results and IQR for glucose concentration in CSF (E), CSF to blood glucose ratio (F), lactate concentration in CSF (G) and CSF to blood lactate ratio (H) on the three days before infection and the first three days of infection. Significant differences are indicated with '*'.



Diagnostic Accuracy of Clinical Signs and Biochemical Parameters for External Ventricular Cerebrospinal Fluid Catheter-Associated Infection

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