RESEARCH ARTICLE OPEN ACCESS

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

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Neurology: Clinical Practice August 2022 vol. 12 no. 4 298-306 doi:10.1212/CPJ.0000000000200059

Abstract

Background and Objectives

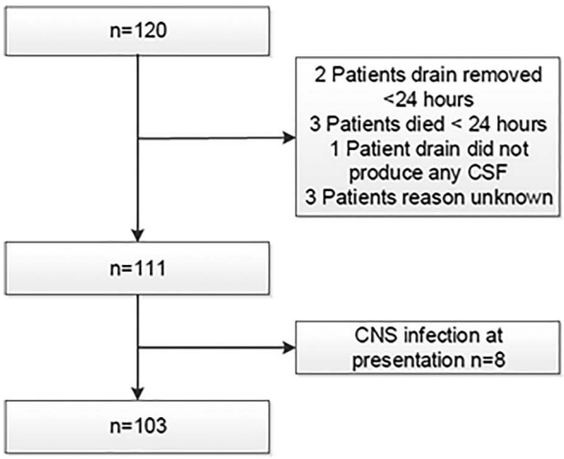
Few prospective well-designed diagnostic accuracy studies have been performed to study the parameters of infection in patients suspected for external ventricular catheter-associated infection. Our objective was to analyze the diagnostic accuracy of clinical characteristics and biochemical and microbiological parameters in diagnosing external ventricular 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 before to 3 days after the day the CSF sample was collected that grew bacteria.

Results

A total of 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 (interquartile range [IQR] +2 to +4). On day 0, none of the tests could differentiate between patients with and without infection. The CSF leukocyte count was increased in patients with ventricular catheter-associated infection as compared with patients without on days +2 and +3. The difference was most prominent on day +2 (1,703 × 10^6/L [IQR 480–6,296] vs 80 × 10^6/L [IQR 27–251]; $p < 0.001$; area under the curve [AUC] 0.87 [95% confidence interval (CI) 0.71–1.00]). Sensitivity for the CSF leukocyte count at a cutoff level >1,000 × 10^6/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 of polymorphonuclear cells (PMNs) was higher in patients with infection on days +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]).



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Class of Evidence
Criteria for rating therapeutic and diagnostic studies
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Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

The Article Processing Charge was funded by the authors.

Discussion

An elevated CSF leukocyte count and increased percentage of PMNs are the strongest indicators for external catheter-associated infections on the days before 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, an elevated CSF leukocyte count and an increased percentage of PMNs are the strongest indicators of catheter-associated infections in the days before CSF culture positivity.

There is a high rate of infection in patients with external ventricular catheters, which has been associated with increased duration of drainage, leakage of CSF 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 (ICU), with a 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 a 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 a 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 CSF catheter-associated infection.

Methods

Patient Population

We performed a single-center observational cohort study including consecutive adult patients admitted to the ICU of the Haaglanden Medical Center (a large nonacademic teaching hospital) with external ventricular CSF catheters. Exclusion criteria were expected death within 24 hours and a CNS 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 and 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, and lactate and glucose concentration. Culture and Gram stain of CSF were 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, United Kingdom) were inserted in an operating theater under sterile conditions with subcutaneous tunneling for several centimeters. Perioperatively, 1,000 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 through 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 and 9 AM). As part of standard care, all patients received selective oropharyngeal decontamination with tobramycin, colistin, and amphotericin 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 neurologic 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 days 6 to 12 after placement).

Statistical Analysis

Variables were expressed as mean with SDs or median with interquartile range (IQR). Group characteristics were compared between patients with and without infection by using the χ^2 test for nominal variables and the Mann-Whitney *U* test for continuous variables. A p value <0.05 was considered significant. We analyzed the predictive value of CSF parameters from 3 days before to 3 days after the diagnosis by comparing values with day 0 and comparing them with the previous day by using the Wilcoxon signed-rank test. We decided to analyze our data up to 3 days before to day 0 to enable the detection of an early infectious response. We performed the analysis up to 3 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 2 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, an elevated CSF leukocyte count and an increased percentage of polymorphonuclear cells (PMNs) are the strongest indicators of catheter-associated infections in the days before CSF culture positivity.

Results

From August 2014 to September 2017, 120 patients received an external ventricular catheter. Seventeen patients were excluded because they presented with CNS 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

Table 1 Patient Characteristics

Characteristics[a]	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[b]	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)	
Perioperative 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

Abbreviations: GCS = Glasgow Coma Scale; IQR = interquartile range.
[a] n/N (%) or median (IQR).
[b] Medical history of currently active cancer (n = 2) or the use of corticosteroids (n = 3).

of unknown reasons (n = 3; eFigure 1, links.lww.com/CPJ/A362).

The median age of the 103 included patients in the analysis was 61 years (IQR 50–70), and 48 patients (47%) were female (Table 1). The admission diagnosis was subarachnoid hemorrhage in 53 patients (51%) and intraventricular or intraparenchymal hemorrhage in 39 patients (38%). The median 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, 1,190 CSF samples of 1,495 days of drainage were available for analysis (80%) and 379 of 496 days between days −3 and +3, with day 0 being the day the culture positive sample was taken (76%).

Fifteen patients (15%) fulfilled the definition of a culture-proven catheter-associated infection (eTable 1, links.lww.com/CPJ/A363). 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 days −3 and +3 in 8 of the 74 patients (11%) without catheter-associated infection who had a catheter in situ between days −3 and +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 the 1,158 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 the 52 culture positive CSF samples (38%) and in 8 of the 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 3 patients (described in eTable 1, links.lww.com/CPJ/A363). In total, 40 of the 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 in 7 of the 15 patients with meningitis (47%).

Clinical Characteristics

Scores on the GCS were comparable between patients with and without infection on day 0 (eTable 2, links.lww.com/CPJ/A364). Body temperature was higher in patients with infection as compared with patients without infection on day +1 (eTable 3, links.lww.com/CPJ/A365). On day +2, a higher proportion of patients with infection had fever (defined as more than 38.0°C) as compared with those without infection (11 of the 13 [85%] vs 21 of the 39 patients [56%]; sensitivity 85% [95% confidence interval (CI) 55%–98%], specificity 46% [95% 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 before and the

Figure 1 Infection Occurrence Over Days

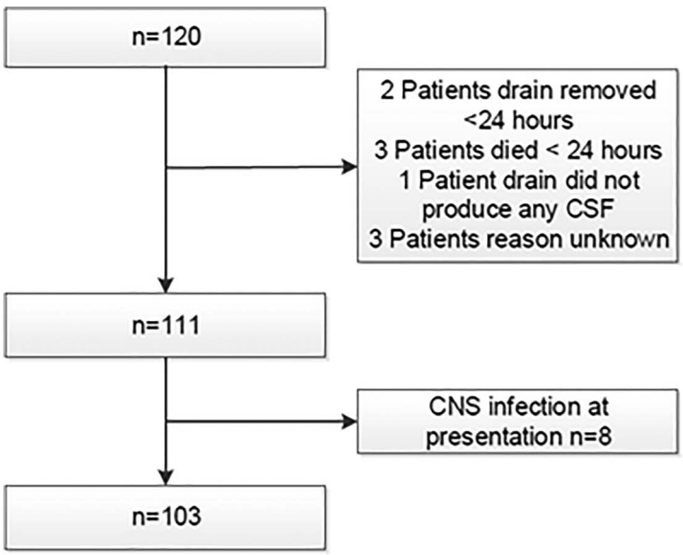


Table 2 Clinical and Biochemical Characteristics Present in Patients With and Without External Ventricular Catheter-Associated Infection: Day 2

	Median patients with infection (IQR)	Median patients without infection[a] (IQR)	*p* Value	AUC (95% CI)	Cutoff	Patients with infection n/N (%)	Patients without infection[a] n/N (%)	Sensitivity[b] % (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 (×10^6/L)	1,703 (480–6,296)	80 (27–251)	<0.01	0.87 (0.71–1.00)	>5	9/9 (100)	32/36 (89)			0.57
					>100	8/9 (89)	15/36 (42)	89 (52–100)	58 (41–74)	0.02
					>1,000	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)			0.61
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)			0.08
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)	0.03
Percentage of PMNs	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)						

Abbreviations: AUC = area under the curve; CI = confidence interval; IQR = interquartile range; PMN = polymorphonuclear cell.
[a] Patients were only included if the drain is in situ on day 11.
[b] Calculated in case a significant difference between patients with and without external ventricular catheter-associated infection was found.

day of sampling of the first positive CSF culture (days −3 to 0; eTable 2, links.lww.com/CPJ/A364, Figures 2 and 3). The CSF leukocyte count was increased in patients with external ventricular catheter-associated infection as compared with patients without on days +2 and +3 (Table 2 and eTable 4, links.lww.com/CPJ/A366). The difference in CSF leukocyte count between patients with and without infection was most prominent on day +2 (1,703 × 10^6/L [IQR 480–6,296] vs 80 × 10^6/L [IQR 27–251]; $p < 0.01$; area under the curve [AUC] 0.87 [95% CI 0.71–1.00]). The cell index was increased in patients with infection on days 1, 2, and 3 (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 eTables 3, links.lww.com/CPJ/A365, and 4, links.lww.com/CPJ/A366).

The glucose concentration in CSF and CSF-to-blood glucose ratio were lower in patients with ventricular catheter-associated infection on day +3 (eTable 4, links.lww.com/CPJ/A366). The percentage of PMNs was higher in patients with infection on days +1 and +2 (Table 2 and eTable 3, links.lww.com/CPJ/A365). 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 7 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 days +2 and +3 (Table 2 and eTable 4, links.lww.com/CPJ/A366). At a cutoff value of ≥0.6 g/L, on day +2, sensitivity was 70% (95% CI 35–93), specificity 72% (95% CI 55–86), positive predictive value (PPV) 41% (95% CI 26–58), and negative predictive value (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), and NPV 92% (95% CI 77–98).

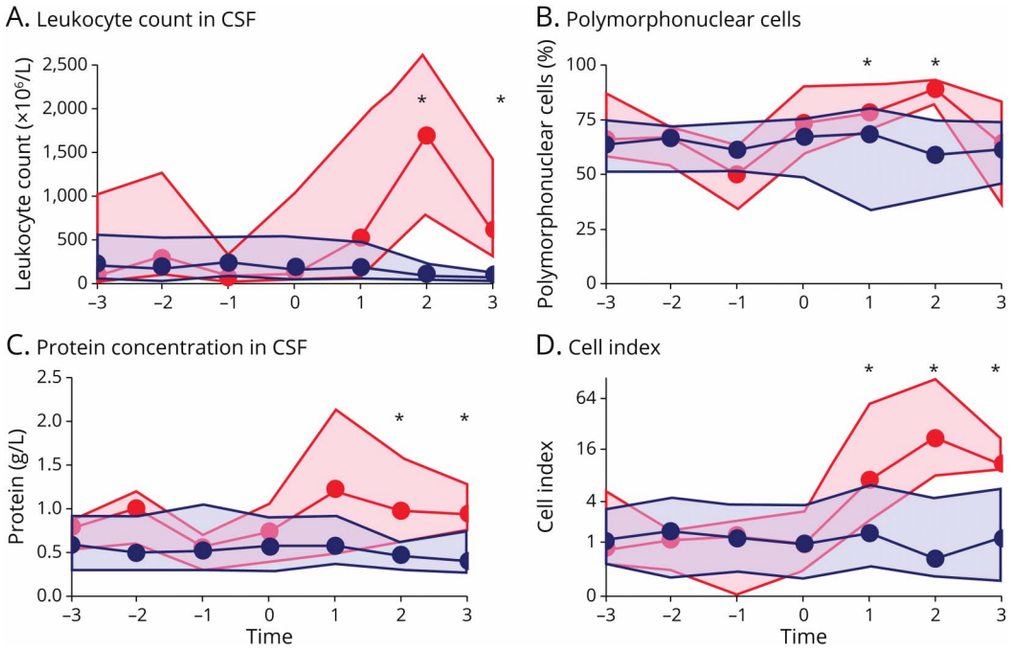
Systemic Markers of Infection

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 with previous days. There was a 4-fold to 5-fold increase in median CSF leucocyte count on day +1 as compared with day

Figure 2 CSF Measures Over Time (Leukocyte Count, % of Polymorphonuclear Cells, Protein Concentration, and Cell Index)



Median results and IQR for leukocyte count in CSF (A), percentage of polymorphonuclear cells (B), total protein concentration in CSF (C), and cell index (D) on the 3 days before infection and the first 3 days of infection. Significant differences are indicated with *. IQR = interquartile range.

0 (529 × 10^6/L [IQR 33–7,430] vs 129 × 10^6/L [IQR 42–1,174]; $p = 0.05$). 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 glucose ratio over time except for the glucose concentration on day +2, which was lower as compared with 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.

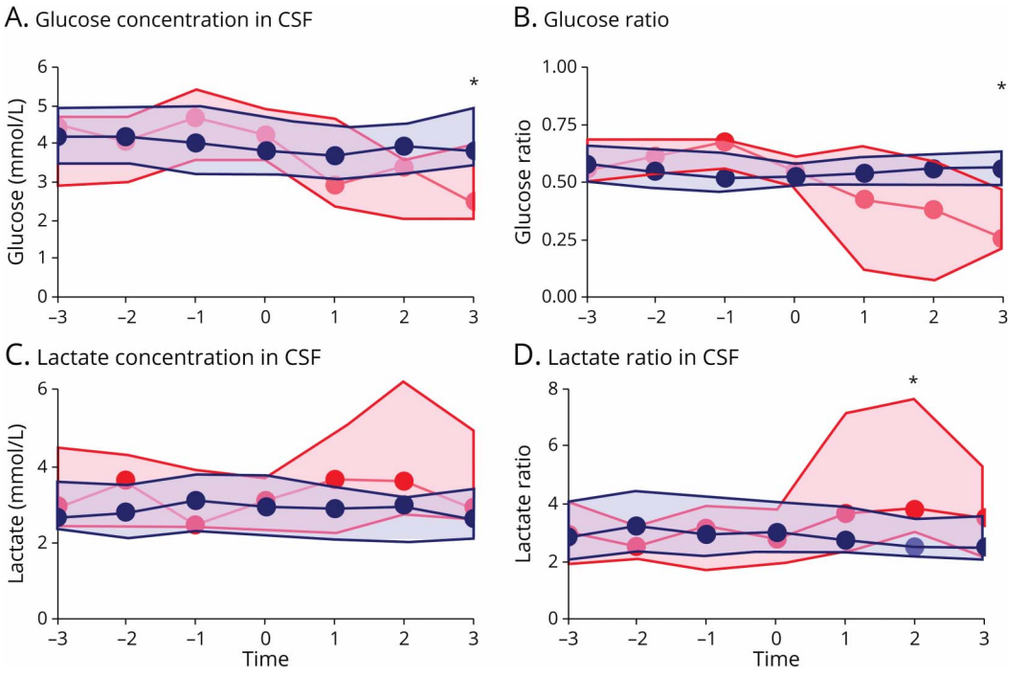
Discussion

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 of PMNs were the strongest indicators for external catheter-associated infections on the days before 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 cutoffs. This was mainly due to blood admixture secondary to the primary neurologic condition and a sterile inflammatory response.[6] Correction for blood admixture by using the cell index provided only a limited incremental value compared with an uncorrected CSF leukocyte count. In previously reported studies, the AUC of the cell index ranged from 0.63 to 0.83, which was comparable with the diagnostic accuracy of the noncorrected leukocyte count.[7-9]

We found that a positive Gram staining is diagnostic for external ventricular CSF catheter-associated infection with a PPV of 100% and could be used to identify 8 of the 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 a specificity of 100%.[10,11] Because of the high specificity, CSF Gram staining should be routinely performed in patients for 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 suspected infections, antibiotic therapy should be initiated. Our results showed a median of 3 days before cultures grew bacteria with a range up to 8 days. This is comparable with a previous study of 158 CSF samples, in which there was a

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 (A), CSF-to-blood glucose ratio (B), lactate concentration in CSF (C), and CSF-to-blood lactate ratio in blood (D) on the 3 days before infection and the first 3 days of infection. Significant differences are indicated with *. IQR = interquartile range.

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 postneurosurgical patients with an elevated leukocyte count.[14] However, in the population of patients with external ventricular CSF catheter-associated infections, this approach seems inappropriate because we found that in 27% of the 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.

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 (odds ratio 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 was lower on day +3 as compared with day 0. Before the removal of the drain, a drain challenge was performed. During the

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 of polymorphonuclear cells are the strongest indicators for external catheter-associated infections on the days before 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.

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 of PMNs 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.

Study Funding

This work was supported by a grant from the Research Fund of Haaglanden Medical Center 2014 (to K.R.I.S.D.); the Jacobus Foundation (to K.R.I.S.D.); the Netherlands Organization for Health Research and Development (ZonMw; NWO-Vidi grant [917.17.308 to M.C.B.]; ZonMw; NWO-Vidi grant 2010 [016.116.358 to D.v.d.B.]; NWO-Vici grant 2019 [918.19.627 to D.v.d.B]; and the European Research Council [ERC Starting Grant 281156 to D.v.d.B.; ERC Consolidator 101001237 grant to M.C.B.]).

Disclosure

The authors report no disclosures relevant to the manuscript. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

Publication History

Received by *Neurology: Clinical Practice* September 20, 2021. Accepted in final form April 28, 2022. Submitted and externally peer reviewed. The handling editor was Editor Luca Bartolini, MD.

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Neurol Clin Pract 2022;12;298-306 Published Online before print July 5, 2022
DOI 10.1212/CPJ.0000000000200059