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ARTICLE

CSF lactate for accurate diagnosis of community-acquired bacterial meningitis

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Abstract CSF lactate measurement is recommended when nosocomial meningitis is suspected, but its value in community-acquired bacterial meningitis is controversial. We evaluated the diagnostic performance of lactate and other CSF parameters in a prospective cohort of adult patients with acute meningitis. Diagnostic accuracy of lactate and other CSF parameters in patients with microbiologically documented episodes was assessed by receiver operating characteristic (ROC) curves. The cut-offs with the best diagnostic performance were determined. Forty-five of 61 patients (74 %) had a documented bacterial (n=18; *S. pneumoniae,* 11; *N. meningitidis,* 5; other, 2) or viral (n=27 enterovirus, 21; VZV, 3; other, 3) etiology. CSF parameters were significantly different in bacterial vs. viral meningitis, respectively (p<0.001 for all comparisons): white cell count (median 1333 vs. 143/mm^3), proteins (median 4115 vs. 829 mg/l), CSF/blood glucose ratio (median 0.1 vs. 0.52), lactate (median 13 vs. 2.3 mmol/l). ROC curve analysis showed that CSF lactate had the highest accuracy for discriminating bacterial from viral meningitis, with a cutoff set at 3.5 mmol/l providing 100 % sensitivity, specificity, PPV, NPV, and efficiency. CSF lactate had the best accuracy for discriminating bacterial from viral meningitis and should be included in the initial diagnostic workup of this condition.

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Introduction

It is estimated that 4,100 cases of bacterial meningitis [1] and 30,000–75,000 cases of viral meningitis [2] occur annually in the United States. Bacterial and viral acute meningitis have a similar clinical presentation, characterized by the classic triad of headache, fever and neck stiffness, and by cerebrospinal fluid (CSF) pleocytosis [3, 4]. Because delayed antibiotic treatment of acute bacterial meningitis is associated with high morbidity and mortality [5, 6], empirical therapy is usually started pending results of microbiological cultures. CSF and blood cultures may identify a bacterial etiology after 24–72 h of incubation. An early and accurate discrimination between bacterial and viral meningitis would reduce unnecessary antibiotic use and length of hospital stay. CSF parameters, which are needed for confirmation of the acute meningitis syndrome, can be used for the etiological diagnosis, but they frequently overlap in bacterial and viral meningitis [7]. Risk scores are

accurate, but their implementation at the bedside in the emergency department may be complex [8, 9].

CSF lactate is a rapid and simple test performed in the majority of routine hospital laboratories. The Infectious Diseases Society of America (IDSA) recommends to measure CSF lactate when evaluating suspected bacterial meningitis in neurosurgical patients, but not for the work-up of community-acquired bacterial meningitis, mainly due to concerns of limited specificity [10].

Studies of CSF parameters are often compromised by the lack of microbiological documentation of presumed viral cases [11, 12]. The aim of the present study was to assess the diagnostic performance of CSF parameters, and particularly CSF lactate, for the discrimination between microbiologically documented bacterial and viral meningitis.

Methods

Patients and setting

We performed the present analysis in a prospective multicenter cohort study of adult patients hospitalized with acute meningitis. This study was designed to validate a diagnostic and therapeutic algorithm for the initial management of meningitis during the period November 2005 to October 2008 at the Lausanne University Hospital, a 1000-bed tertiary center, and in four university-affiliated hospitals of Western Switzerland [13].

The algorithm based on guidelines, evidence from the literature and local epidemiology proposed a standardized upfront clinical management for suspected bacterial meningitis. The indications for and sequential timing of lumbar puncture, empirical antibacterial therapy, cerebral CT scan, and corticosteroid therapy were established according to the severity of the clinical presentation [13].

For the present study, only patients with microbiologically documented acute meningitis fulfilling all the following criteria were included: (1) clinical presentation with at least one of the following symptoms/signs: fever, headache, neck stiffness, impaired level of consciousness, (2) CSF pleocytosis (i.e., >4 white blood cells/mm^3), and (3) microbiological documentation of the etiology (for bacterial meningitis: positive Gram stain, culture or PCR in the CSF and/or positive blood culture; for viral meningitis: positive CSF PCR or positive blood serology). Patients were excluded if they were <16 years old, if no LP was performed, if they had a nosocomial meningitis according to CDC criteria [14], or had a neurosurgical shunt.

The study was approved by the local Institutional Review Board [Commission cantonale d'éthique de la recherche sur l'être humain (CER-VD), Lausanne, Switzerland].

Data collection

Data on patient's demographics and baseline characteristics, clinical presentation of meningitis, blood and CSF laboratory parameters, microbiological documentation, antibacterial and corticosteroid therapy, and length of ICU and hospital stay were prospectively collected. Patient's outcome was assessed by overall in-hospital mortality and neurological disability score at discharge (Glasgow Outcome Score [15]).

Diagnostic CSF work-up included measurement of leucocyte and neutrophil count, protein (Pyrogallol red method, Randox Laboratoiries, Schwyz, Switzerland), glucose (enzymatic hexokinase test, Roche Diagnostics, Rotkreuz, Switzerland) and lactate (enzymatic lactate oxidase test, Roche Diagnostics, Rotkreuz, Switzerland). The following microbiological tests were systematically performed on the CSF in all patients presenting with acute meningitis during the study period: (1) Gram stain, (2) bacterial culture, (3) a multiplex real-time bacterial PCR targeting the four most frequent pathogens of community-acquired bacterial meningitis (*Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae* and *Listeria monocytogenes),* (4) real-time viral PCR for enterovirus and herpes-simplex virus 1 and 2. The bacterial PCR was developed at our institution by combining the multiplex PCR described by Corless et al. [16] and a real-time PCR detecting *Listeria monocytogenes* targeting the virulence gene *hly* encoding the hemolysin listeriolysin [17]. Homemade viral PCRs were used [13]. Complementary diagnostic procedures were applied according to the clinical history and presentation: real-time CSF PCR for varicella-zoster virus, blood serologies for viruses (e.g., human immunodeficiency virus, tick-borne encephalitis virus) and bacteria (e.g., *Borrelia burgdorferi*, syphilis).

Data analysis

The diagnostic accuracy of CSF leucocyte count, neutrophil count, proteins, CSF/blood glucose ratio, and lactate for differentiating bacterial from viral meningitis was assessed by receiver operating characteristics (ROC) curves and by calculating sensitivity, specificity, positive and negative predictive values as well as efficiency after having identified the optimal cut-off (point with the shortest distance to the left upper corner of the ROC curve). Continuous variables were compared by the Mann–Whitney test and categorical variables by the Fisher's exact test. The two-tailed level of statistical significance was set at 0.05. STATA software, version 12.1 (StataCorp, College Station, TX, USA), and GraphPad Prism, version 6.0 (GraphPad Software, Inc., San Diego, CA, USA) were used for data analysis.

Results

Patients' demographics, clinical characteristics and outcome

Among 111 patients screened for inclusion in the prospective cohort study, 61 fulfilled the diagnostic criteria for acute meningitis. Thirteen patients in whom microbiological documentation was lacking and three in whom LP was not performed because of contraindications (coagulopathy and thrombocytopenia in two; intracranial hypertension in one) were excluded from the present analysis. Among 45 patients with microbiologically documented meningitis, 18 had bacterial meningitis (*Streptococcus pneumoniae, n*=11; *Neisseria meningitidis*, *n*=5; *Haemophilus influenzae*, *n*=1, and *Streptococcus agalactiae*, *n*=1). The bacterial etiology was documented by cultures in 11 patients (blood, *n*=11; CSF, *n*=10), and by real-time CSF PCR in the remaining seven cases. The following etiologies were documented in 27 patients with viral meningitis: enterovirus in 21 (positive CSF PCR), varicella-zoster virus in three (positive CSF PCR), tick-borne encephalitis virus in two (positive blood serology), and herpes simplex virus type 2 in one (positive CSF PCR).

Patients' demographics and clinical characteristics at time of admission in the Emergency department are summarized in Table 1. As compared to patients with viral meningitis, patients with bacterial meningitis had a shorter time elapsed between onset of symptoms and hospital admission (median 24 vs. 42 h, p=0.03), a higher rate of neck stiffness (17 out of 18, 94 % [95 % confidence interval (CI) 73–100] vs. 18 out of 27, 67 % [95 % CI 46–83], p=0.03), a lower Glasgow Coma Scale (median 12 vs. 15, p<0.001), a higher white blood cell count (median 17 vs. 9.1 G/l, p<0.001) and a higher median C-reactive protein (117 vs. 8.5 mg/l, p<0.001). Rates of ICU admission (14 out of 18, 78 % [95 % CI 52–94] vs. 1 out of 27, 4 % [95 % CI 1–19], p<0.001) and overall in-patient mortality (6 out of 18, 33 % [95 % CI 1–57] vs. 0 [95 % CI 0–0], p=0.002) were also significantly higher in patients with bacterial meningitis as compared to those with viral meningitis. A significantly higher percentage of patients with bacterial meningitis had a compromised neurological outcome, as assessed by a Glasgow Outcome Scale less than 5 (8 out of 14, 57 % [95 % CI 29–82] vs. 2 out of 23, 9 % [95 % CI 1–28], p=0.002).

CSF parameters and their diagnostic accuracy

CSF parameters in patients with bacterial and viral meningitis are compared in Fig. 1 (panel A to E). Median CSF white cell and absolute neutrophil counts, and median CSF protein and lactate concentrations were significantly higher in bacterial meningitis, while CSF/blood glucose ratio was higher in viral meningitis. Median CSF lactate concentrations were 13 mmol/l in bacterial and 2.3 mmol/l in viral meningitis. In contrast to the other CSF parameters, no overlap for values of CSF lactate was observed between the two groups.

No correlation was found between CSF lactate concentrations and time elapsed between onset of meningitis symptoms and hospital admission or administration of the first antibiotic dose. Univariate analysis in bacterial meningitis did not show any association between CSF lactate concentrations and mortality or ICU admission. However, there was a non-significant trend toward higher lactate concentrations among bacterial meningitis patients with a Glasgow Outcome Scale lower than five (median 13.95 mmol/l) as compared to those with a Glasgow Outcome Scale of 5 (median 9.3 mmol/l, p=0.057).

The diagnostic accuracy of the CSF parameters was tested by ROC curve analysis (Fig. 2, panel A to E). The area under the curve (AUC) of CSF leucocyte count, neutrophil count,

Table 1 Demographic, clinical and cerebrospinal fluid (CSF) characteristics in patients with microbiologically documented bacterial or viral meningitis

Characteristic	Bacterial meningitis (*n*=18)	Viral meningitis (*n*=27)	*P*-value
Median age, years (range)	53 (17–86)	35 (17–77)	0.1
Female gender (%)	9 (50)	12 (44)	0.5
Median time elapsed between onset of symptoms and hospital admission, hours (range)	24 (2–120)	42 (9–240)	0.03
Antibiotic therapy before admission (%)	2 (11)	6 (22)	0.4
Headache (%)	15 (83)	27 (100)	0.06
Fever (%)	14 (78)	23 (85)	0.7
Neck stiffness (%)	17 (95)	18 (67)	0.03
Median Glasgow Coma Scale (range)	12 (4–15)	15 (12–15)	<0.001
Median blood white blood cell count, G/L (range)	17 (1.3-35.0)	9.1 (4.4-14.0)	<0.001
Median blood C-reactive protein, mg/L (range)	117 (12–450)	8.5 (2–103)	<0.001
ICU admission (%)	14 (78)	1 (4)	<0.001
Overall in-patient mortality (%)	6 (33)	0	0.002
Glasgow outcome scale <5 (%)	8/14 (57)	2/23 (9)	0.002

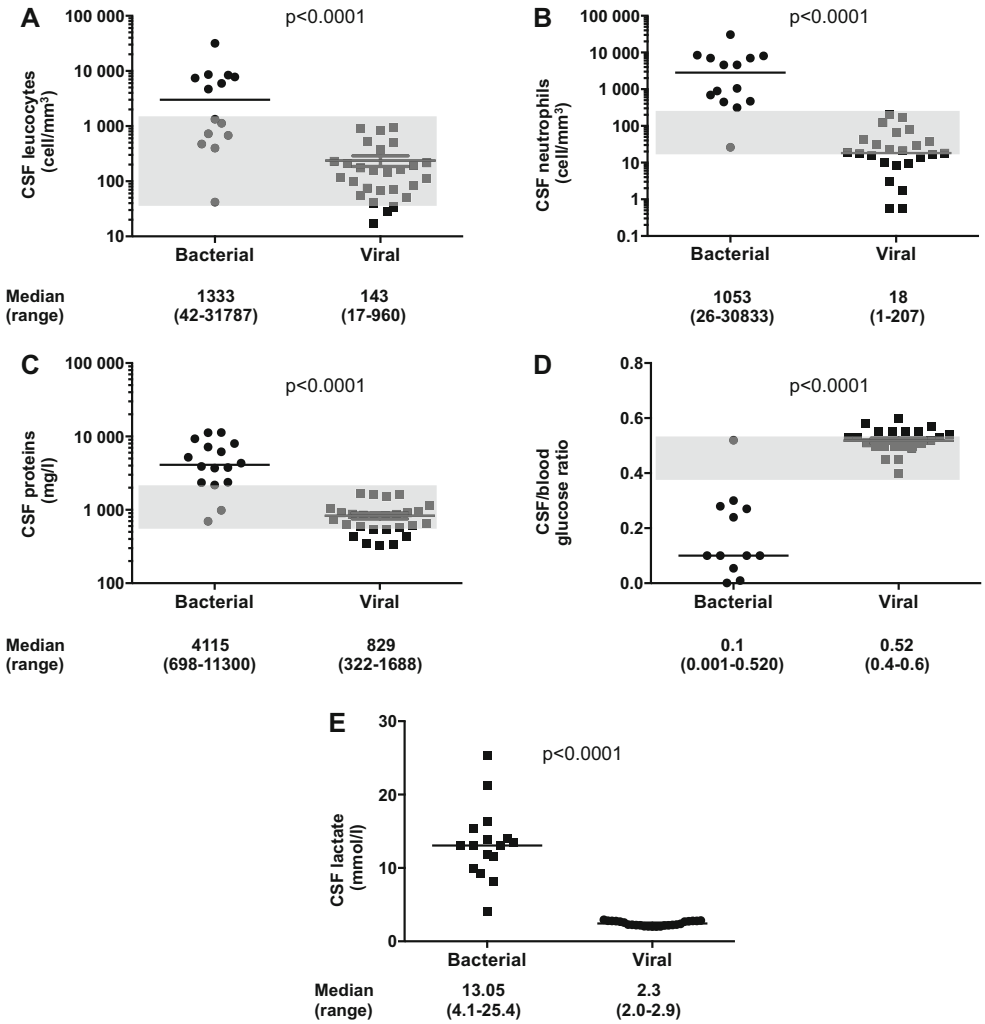

Fig. 1 Comparison of CSF parameters between microbiologically documented bacterial and viral meningitis. Cerebrospinal fluid (CSF) parameters in patients with microbiologically documented bacterial or viral meningitis: leucocytes (panel **A**), absolute neutrophil count (panel **B**), proteins (panel **C**), CSF/blood glucose ratio (panel **D**), lactate (panel **E**). Intervals of values overlapping between the two conditions are highlighted in grey

and proteins concentration was 0.89 (95 % confidence interval 0.76–1), 0.97 (95 % CI 0.91–1), and 0.95 (95 % CI 0.88–1), respectively. The AUC of CSF/blood glucose ratio was 0.96 (95 % CI 0.88–1), while the AUC of CSF lactate was 1 (95 % CI 1–1), with 100 % sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and efficiency at a CSF lactate cut-off value of 3.5 mmol/l (Table 2) for distinguishing bacterial from viral meningitis. Sensitivity, specificity, PPV, NPV and efficiency at the best cut-offs of the other CSF parameters are reported in Table 2. These figures were almost identical when data from patients lacking microbiological evidence were included in the analysis.

Discussion

This analysis in a prospectively studied cohort of patients with microbiologically documented acute meningitis suggests that CSF lactate has an excellent diagnostic accuracy for discriminating a bacterial from a viral etiology. The ROC curve analysis showed an area under the curve of 1, and a CSF lactate cut-off of 3.5 mmol/l had 100 % sensitivity, specificity, PPV, NPV, and efficiency.

The majority of routine hospital laboratories can provide measurement of CSF lactate values within a few minutes after reception of the clinical sample. By contrast to glucose, simultaneous measurements of lactate in CSF and blood are not needed, as CSF lactate levels are independent from blood levels [18]. Elevated CSF lactate in acute bacterial meningitis results from anaerobic brain metabolism related to brain edema, reduced cerebral blood flow [19], and inflammatory cytokines [20]. Guerra-Romero et al. studied central nervous system lactate production in a rabbit model of pneumococcal meningitis [21]. By measuring lactate concentrations with in situ brain microdialysis, these authors showed that sources of elevated CSF lactate were the cortex and hippocampus rather than the subarachnoid space or the

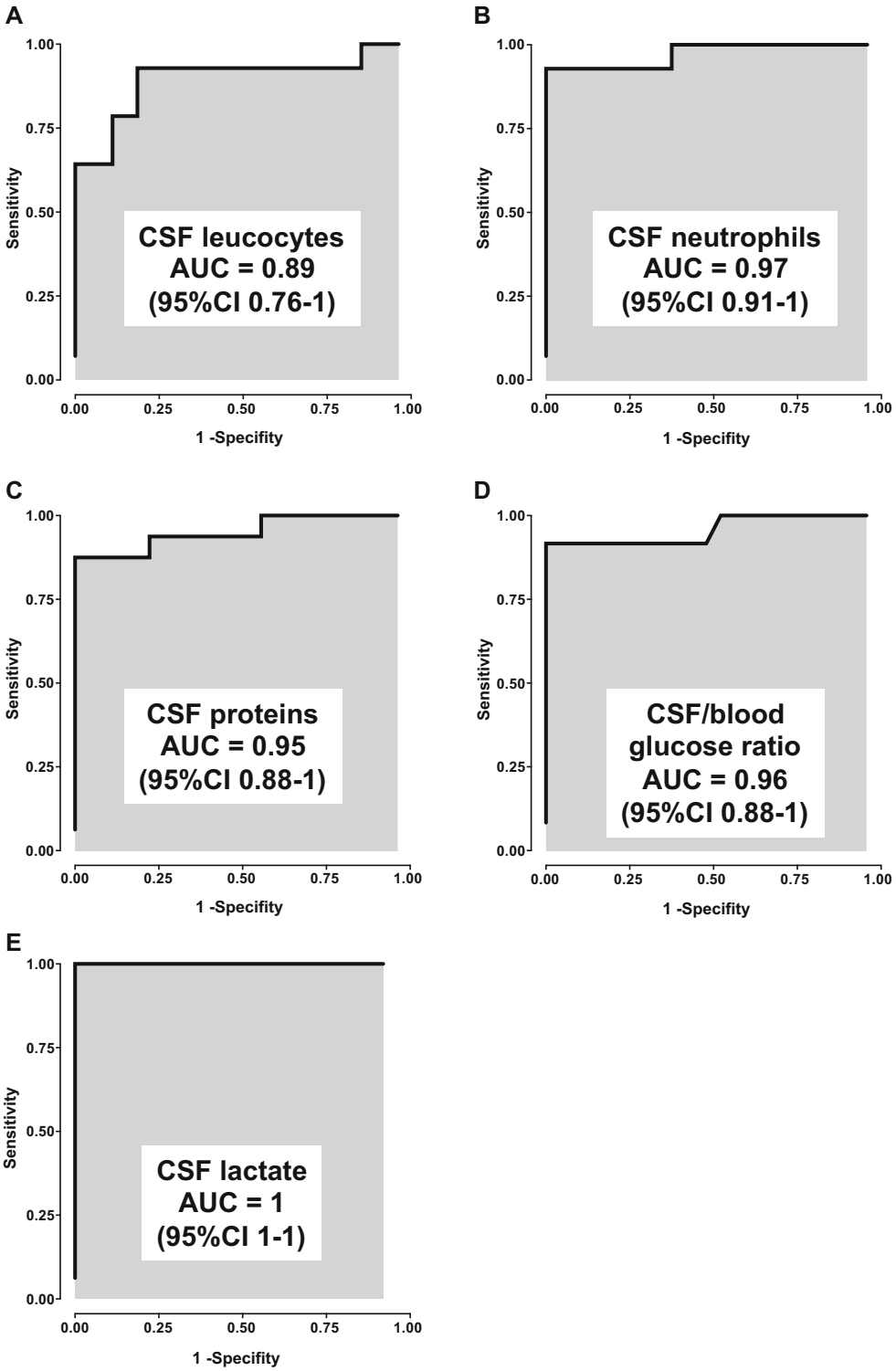

Fig. 2 ROC curve analysis of CSF parameters. Receiver operating characteristics (ROC) curve analysis of cerebrospinal fluid (CSF) parameters for the diagnosis of bacterial meningitis: leucocytes (panel **A**), absolute neutrophil count (panel **B**), proteins (panel **C**), CSF/blood glucose ratio (panel **D**), lactate (panel **E**)

blood [21]. Elevated lactate levels are also found in other infectious or non-infectious neurological disorders such as cerebral malaria [22], seizures, ischemia, hemorrhage [23], but not in viral meningitis. Therefore, in the setting of the acute meningitis syndrome, in which non-infectious causes of elevated CSF lactate concentrations are not considered in the differential diagnosis, CSF lactate may be helpful to distinguish bacterial from viral meningitis.

The diagnostic accuracy of CSF lactate compared to that of other CSF parameters was demonstrated in post-neurosurgical meningitis [24, 25]. In a retrospective study of 73 patients with suspected bacterial meningitis occurring

Table 2 Accuracy of cerebrospinal fluid (CSF) parameters for the diagnosis of bacterial meningitis. Performance data of the best cut-off for each parameter (value indicated in parentheses in the left column) are shown

Parameter	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Efficiency (%)
Leucocytes (>388 cells/mm³)	81 (62–94)	92 (64–100)	75 (48–93)	96 (78–100)	87
Neutrophils (>260 cells/mm³)	92 (64–100)	100 (86–100)	100 (74–100)	96 (80–100)	97
Proteins (>1934 mg/l)	88 (62–98)	100 (87–100)	100 (77–100)	93 (77–99)	95
CSF/blood glucose ratio (<0.35)	92 (62–100)	100 (85–100)	100 (71–100)	96 (79–100)	97
Lactate (>3.5 mmol/l)	100 (79–100)	100 (86–100)	100 (79–100)	100 (86–100)	100

PPV positive predictive value, *NPV* negative predictive value

Ninety-five percent confidence intervals (95% CI) for each performance parameter are reported in parentheses

after neurosurgery, sensitivity and specificity of CSF lactate at a cut-off of 4 mmol/l and of CSF/blood glucose ratio at a cut-off of 0.4 were 88 % vs. 77 % and 98 % vs. 87 %, respectively [25]. Based on this study, guidelines of the IDSA recommend the use of CSF lactate for the diagnosis of post-neurosurgical bacterial meningitis and the initiation of empirical antibacterial therapy if CSF lactate level is ≥4 mmol/l [10].

In contrast, IDSA guidelines do not recommend routine CSF lactate measurement for the diagnosis of community-acquired bacterial meningitis. Due to the lack of specificity of CSF lactate, experts consider that it does not provide clinically meaningful additional information when CSF leucocytes, proteins, and glucose values are known. Nevertheless, studies in patients with acute meningitis have shown that CSF lactate is a better marker of a bacterial etiology than CSF leucocytes, neutrophils, or glucose [26–31]. A meta-analysis of 25 studies found a diagnostic odds ratio of 270 (95 % CI 142–519) of CSF lactate at a cut-off value of 3.5 mmol/l for the diagnosis of bacterial meningitis [11]. A recent study from Uganda validated CSF lactate as a useful point-of-care test for rapid diagnosis of bacterial meningitis [32]. Importantly, the lack of microbiological documentation in culture-negative meningitis of presumed viral etiology is a common limitation in the majority of the above-mentioned studies that have been performed in the pre-molecular diagnostic era. In these reports, the definition of possible viral meningitis was generally based on the combination of a clinical presentation lacking severity criteria and negative bacterial cultures [12, 26]. However, bacterial cultures are typically negative when empirical antibacterial therapy is administered before lumbar puncture. A better indirect diagnostic criterion for viral meningitis would be a good clinical outcome in the absence of antibacterial treatment, but the large majority of patients with acute meningitis are treated empirically with high-dose antibiotics pending culture results. To avoid the bias resulting from cases of aseptic meningitis without ascertained etiology, we included only microbiologically documented cases of bacterial and viral meningitis. Furthermore, data were collected prospectively in the study cohort and CSF molecular diagnostic tests were used systematically.

The main limitation of this analysis is the relative small sample of patients. As a consequence, rarer meningitis pathogens were not represented and large confidence intervals prevented a direct comparison of the diagnostic performance between CSF parameters. The clinical efficiency and safety of using a low CSF lactate level (<3.5 mmol/l) to rule out a bacterial etiology and withhold empirical antibiotics in acute meningitis without severity criteria needs to be confirmed in larger patient populations.

In conclusion, this analysis of a prospective cohort of microbiologically documented acute meningitis showed that CSF lactate has an excellent diagnostic accuracy for differentiating bacterial from viral meningitis. The inclusion of this simple, rapid and inexpensive CSF test in the initial diagnostic workup of acute meningitis may simplify the immediate empirical management by reliably distinguishing potentially life-threatening from self-healing infections.

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Conflict of interest The authors declare no competing financial interest in relation to the manuscript.

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