ORIGINAL ARTICLE JIACM 2022; 23 (3-4): 100-104

# CSF Lactate: An Equal Diagnostic but a Superior Prognostic Marker Than CSF Cortisol in Acute Bacterial Meningitis

*Manish Kumar Bansal*, PK Maheshwari**, Tej Pal Singh*, Paramjeet****

## Abstract

***Objective: Meningitis remains a serious clinical problem in developing countries. Delayed diagnosis and treatment result in significant morbidity and mortality. Case fatality can be as high as 25% in bacterial meningitis. Early antibiotic therapy is crucial for improving the outcome of bacterial meningitis. There is a need for a reliable and cost effective method to differentiate among various types of meningitis. There is a need for a test which can distinguish bacterial meningitis from other meningitis during the acute phase of the disease, so as to avoid complications due to delayed treatment. Apart from this, a test which predicts the ultimate prognosis in such type of patients is also needed. Thus, determination of unstimulated endogenous CSF-cortisol and CSF lactate activity may be an early diagnostic and prognostic marker in bacterial meningitis patients and to determine the cut-off level of cortisol and lactate for the diagnosis of bacterial meningitis.***

***Methods: Adults with clinical findings compatible with meningitis and no prior treatment were studied. Seventy patients with conventional CSF parameters consistent with acute bacterial meningitis were evaluated. CSF lactate and CSF cortisol were recorded.***

***Results: The peak incidence of bacterial meningitis was seen in the 36 - 40 years age group and the mean Glasgow Coma Scale score on admission was 4.35. The mean cortisol concentration in cerebrospinal fluid (CSF) was 159 (59 to 277) nmol/l and the mean CSF lactate concentration was 8.8 (5.6 to 12.1) mmol/l. Furthermore, CSF lactate levels correlated with Glasgow Coma Scale score (f = 11.635, P = < 0.0001) but not the CSF cortisol levels (f = 2.008, P = 0.104). The CSF cortisol concentration of 50 nmol/l and CSF lactate concentration of 3 mmol/l was found to be the optimal cut-off values for diagnosis of bacterial meningitis.***

***Conclusion: CSF cortisol levels and CSF lactate levels in patients with bacterial meningitis are highly elevated and may serve as valuable marker in diagnosing bacterial meningitis. Furthermore, CSF Lactate but not CSF cortisol correlate with disease severity.***

***Key words: Bacterial meningitis, CSF lactate, CSF cortisol, Glasgow coma scale.***

## Introduction

Meningitis is an inflammation of the leptomeninges and underlying subarachnoid cerebrospinal fluid (CSF). So, bacterial meningitis is a common infectious disease of the CNS in developing countries like India, and also a major global health problem even in the developed world. Its causative organisms mainly Pneumococcus, haemophilius influenza and meningococcus have a worldwide distribution. It represents a serious disease associated with significant morbidity and mortality[1]. Furthermore, long-term sequelae such as hearing loss, palsies, and personality changes affect approximately 40% of survivors[2].

Signs and symptoms, results of routine CSF analysis and radiological finding are often inadequate in making a definitive diagnosis. Gram's stain and AFB stain of CSF are rapid methods of detection of the pathogenicorganism, but lack sensitivity. Similarly, culture of CSF is another method of diagnosis, but it is time consuming. PCR test is a highly sensitive and specific test, but is very costly and not widely available. There is a need for a test which can distinguish bacterial meningitis from other meningitis during the acute phase of the disease, so as to avoid complications due to delayed treatment. Apart from this, a test which predicts the ultimate prognosis in such types of patients is also needed.

In view of all these limitations, determination of CSF-cortisol and CSF-lactate activity may be a valuable marker in diagnosing bacterial meningitis and also determining its prognostic value in these patients. The main purpose of this study is to evaluate utility of CSF cortisol and CSF lactate in bacterial meningitis.

## Material and Method

This was a prospective study including adults more than 16 years of age, who presented to the emergency department of the Sarojini Naidu Medical College, Agra during the

***Professor, ***3rd Year Resident, Department of Medicine, **Professor, Department of Neurology, Sarojini Naidu Medical College, Agra - 282 002, Uttar Pradesh.***
***Corresponding Author: Dr Manish Kumar Bansal, Professor, Department of Medicine, Sarojini Naidu Medical College, Agra - 282 002, Uttar Pradesh. Tel: 9358496016, E-mail: drbansaksn@rediffmail.com.***

period between Sept 2018 to March 2020 with clinical findings consistent with meningitis, (e.g., fever, headache, vomiting, nuchal rigidity, and impaired consciousness). Blood samples were drawn and a lumbar puncture was performed after initial clinical assessment. Biochemical and cytological examination of CSF samples were performed, including the measurement of leukocyte counts, neutrophil counts, glucose level, protein. Only those patients who were diagnosed as having acute bacterial meningitis on the basis of conventional CSF parameters were included (Fig. 1) in the study. CSF lactate, CSF cortisol and culture for bacterial meningitis was done. In blood samples collected at the same time, serum leukocyte count, serum glucose, and blood culture were done. The exclusion criteria comprised partially treated cases (which included treatment with antibiotics and steroids), traumatic lumbar punctures for CSF collection, meningitis in HIV patients, or those who were on ART.

Once the diagnosis of bacterial meningitis was made, the following data were recorded: demographics (age, gender, weight), total number of patients admitted, medical history, clinical findings, and the results of the tests performed.

Reference values for CSF-cortisol: 8 - 12 nmol/l or,

Normal – < 2 µg/dl

Nonbacterial – 2 - 10 µg/dl

Bacterial[3] – > 10 µg/dl

Reference values for CSF-lactate: 0.9 - 3.0 mmol/l.

The clinical outcome and neurological disability of the patients was assessed using GLASGOW OUTCOME SCORE (Table I). The study was approved by the hospital's ethical committee. A written informed consent was obtained from all parents/guardians. SPSS (SPSS Statistics for Windows, Version 20.0, NY, USA) and XLSTAT 2016 (Microsoft® Excel/ XLSTAT© 2016, Addinsoft, Inc., Brooklyn, NY, USA) were used for statistical analysis. The Chi-square test was applied and $p < 0.05$ was taken as statistically significant. The results were expressed as means and standard deviation. Prognostic efficiency of CSF lactate and CSF cortisol was analysed using Chi-square test.

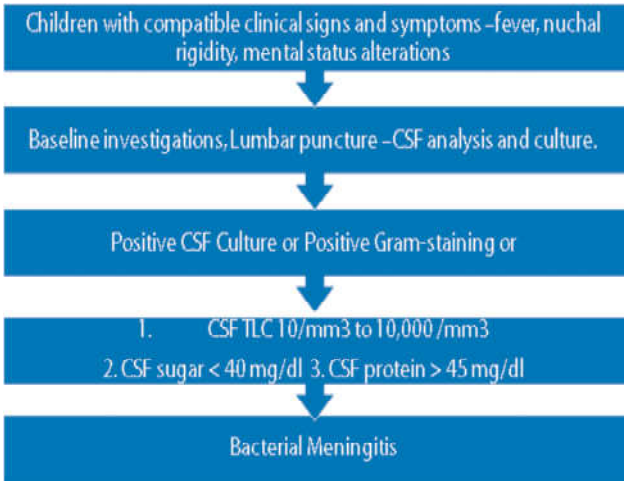


***Fig. 1:*** *Flow chart for diagnosing bacterial meningitis in adults. CSF, cerebrospinal fluid; TLC, total leukocyte count.*

**Table I: Glasgow Outcome Score (GOS).**

| Score | Description |
|---|---|
| 1. | Death |
| 2. | Persistent Vegetative State: Patient exhibits no obvious cortical function. |
| 3. | Severe disability: Conscious but disabled. Patient depends on others for daily support. |
| 4. | Moderate disability: Disabled but independent. Patient is independent as far as daily life. Disabilities include varying degrees of dysphasia, hemiparesis or ataxia as well as intellectual and memory deficits and personality changes. |
| 5. | Good recovery: Resumption of normal activities even though there may be minor neurologic or psychologic deficits. |

## Results

During the study period, among the clinically suspected meningitis patients, 70 patients were diagnosed as acute bacterial meningitis. The demographics, clinical and CSF parameters are summarised in Table II. The mean CSF lactate in bacterial meningitis study population was 8.81 with a Standard Deviation of 2.3 mmol/l, and the minimum and maximum values were 5.6 and 12.1 mmol/l respectively.

The mean CSF Cortisol level in bacterial meningitis study population was 159.43 nmol/l with a Standard Deviation of 62.12, and the minimum and maximum values were 59.0 and 277.0 nmol/l respectively.

CSF culture was positive in 26 (37.14%) patients. The following bacteria were identified in CSF cultures: *Streptococcus pneumoniae*[11] and *Neisseria Meningitidis*[15]. The mean CSF lactate (Table III) in patients with positive and negative CSF culture were 10.31 ± 1.75 (6.6 - 12.10) and 7.92 ± 2.12 (5.6 - 12.10) mmol/l, respectively ($p < 0.0001$). There was statistically significant difference observed in CSF lactate concentrations between patients with CSF culture positive and negative meningitis.

There was a significant statistical difference in CSF Cortisol levels ( Table IV) in culture-positive bacterial meningitis and culture-negative bacterial meningitis. The mean CSF Cortisol was lower in culture-positive bacterial meningitis (140.96 ± 48.38) as compared to culture-negative bacterial meningitis (170.35 ± 62.32) with a p value of 0.0429.

**Table II: Demographic, clinical and CSF characteristics of the patients.**

| Variable | n = 70 |
|---|---|
| Age, years | 33.44 (21 - 41) |
| M/F | 49/21 |
| Fever | 70 (100%) |
| Vomiting | 37 (52.85%) |
| Signs of meningeal irritation | 70 ( 100%) |
| Mental status changes | 23 (32.85%) |
| Convulsions | 10 (14.28%) |
| Focal deficit (Hemiparesis) | 3 (4.28%) |
| 6th CN palsy | 5 (7.14%) |
| CSF TLC/mm$^3$ | 1713 (705 - 3814) |
| CSF protein (mg/dl) | 440 (230 - 630) |
| CSF glucose (mg/dl) | 30.06 (10.8 - 53.6) |
| CSF lactate (mmol/l) | 8.8 (5.6 - 12.1) |
| CSF cortisol (nmol/l) | 159 (59 - 277) |
| CSF culture positivity | 26 (37.14%) |
| Glasgow outcome score (mean ) | 4.35 |
| Outcome (death at day 28; n) | 4 |

*CSF: Cerebrospinal fluid; CN: Cranial nerve; TLC: Total leukocyte count.*

**Table III: Microbiological corelation of CSF lactate (mmol/l) levels in bacterial meningitis study population.**

| | CSF lactate (mmol/l) | |
|---|---|---|
| | Culture and/PCR positive | Culture and/PCR negative |
| N | 26 | 44 |
| Mean ± SD | 10.31 ± 1.75 | 7.92 ± 2.12 |
| Mini. | 6.6 | 5.6 |
| Max. | 12.10 | 12.10 |

*t-value = -4.850; p-value = < 0.0001.*

**Table IV: Microbiological corelation of CSF cortisol levels in bacterial meningitis study population.**

| | CSF cortisol (nmol/l) | |
|---|---|---|
| | Culture and/PCR positive | Culture and/PCR negative |
| N | 26 | 44 |
| Mean ± SD | 140.96 ± 48.38 | 170.35 ± 62.32 |
| Mini. | 59 | 69 |
| Max. | 248 | 277 |

*t-value = 2.063; p-value = 0.0429.*

**Table V: Mean levels of CSF lactate (mmol/l) in respective GOS were as follows.**

| CSF lactate | Glasgow Outcome Score (GOS) | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| n | 4 | 3 | 5 | 10 | 48 |
| Mean ± SD | 11.28 ± 1.40 | 11.90 ± 0.17 | 11.50 ± 0.94 | 10.17 ± 1.36 | 7.85 ± 1.99 |
| Mini. | 9.2 | 11.7 | 9.9 | 7.1 | 5.6 |
| Max. | 12.10 | 12 | 12.10 | 11.7 | 12.0 |

*f-value = 11.635; p-value = < 0.0001; CD = 0.81.*

There was a significant statistical difference in mean CSF lactate levels in different Glasgow outcome score patients. The mean CSF lactate was lower in patients with GOS-5 as compared to patients with GOS-1 with a p value of < 0.0001.

It shows that CSF lactate levels had significant relationship with the prognosis of the patients, levels being less raised in patients with improved outcome and more raised in patients with worse outcome.

**Table VI: Mean levels of CSF cortisol (nmol/l) in respective GOS were as follows.**

| CSF cortisol | Glasgow Outcome Score (GOS) | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| n | 4 | 3 | 5 | 10 | 48 |
| Mean ± SD | 146.25 ± 65.96 | 223.67 ± 30.02 | 132.40 ± 71.30 | 127.10 ± 53.54 | 166.06 ± 61.20 |
| Mini. | 93 | 189 | 59 | 59 | 73 |
| Max. | 238 | 241 | 238 | 202 | 277 |

*f-value = 2.008; p-value = 0.104.*

There was no significant statistical difference in mean CSF cortisol levels in different Glasgow outcome score patients (p value 0.104).

It shows that CSF cortisol levels had no significant relationship with the prognosis of the patients.

## Discussion

The neurological outcomes of Bacterial Meningitis (BM) are often poor, making the early diagnosis and treatment important[5]. Nuchal rigidity, fever, and altered mental state are among the most commonly reported signs and symptoms in adults with BM[6], although one or more of these signs and symptoms is commonly absent[7,8]. We reported fever (100%) as the most commonly presenting symptom, followed by headache (74.3%) and vomitting (37%). In the present study, the classical triad (fever, nuchal rigidity, and altered mental status) was observed only in 23% of patients with BM. Van de Beek *et al*, reported that all

the three features were present in only 44% of 696 adults with proven BM[9], but the absence of all three excluded the diagnosis, with a sensitivity of 99%. Berkley *et al*, observed that 50% to 90% of patients with BM reported neck stiffness[10]. Thomas *et al* further concluded that the poor diagnostic value of neck stiffness is not improved by the presence of Kernig's or Brudzinski's signs, because neither has a sensitivity of more than 10%[7]. The present results showed that, overall, clinical history and examination have a low diagnostic accuracy when used alone. This observation is in agreement with the findings of earlier studies in children and adults[11,12]. Therefore, the onus of final diagnosis lies on CSF examination and bacterial isolation through cultures, in a clinically compatible case. Nigrovic *et al*, reported that the combined assessment of history, CSF microscopy, and CSF biochemistry had a sensitivity of 100% and a specificity of 66% in differentiating between BM and VM in children[13]. However, the atypical manifestation of CSF examination, including culture negative and negative Gram-staining, can result in a missed diagnosis of BM. Studies in adults have indicated that adding CSF lactate to routine CSF examination is better in estimating the chance of BM in a very short time[12,14]. The mechanism of the increase in concentration of lactate in the CSF of patients with meningitis is not clear, but it has been linked with anaerobic glycolysis of brain tissue due to a decrease cerebral blood flow and oxygen uptake[15]. In the present study, a statistically significant increase in CSF lactate was observed in patients with BM. A cut-off value of 3 mmol/l for CSF lactate was found to be optimal for diagnosing bacterial meningitis. The cut-off values studied for CSF lactate concentration ranged from 2.1 to 4.44 mmol/l, in different studies in adults and children[14,16]. Although the epidemiology of BM differs by age[17], the diagnostic value of CSF lactate is similar between children and adults[12]. Huy *et al*, in a systemic review on assessment of CSF lactate concentration to distinguish BM from aseptic meningitis, reported a sensitivity ranging from 0.86 to 1.00 (mean: 0.96; 95% CI: 0.95 - 0.98), and a specificity that varied widely from 0.43 to 1.00 (mean: 0.94; 95% CI: 0.93 - 0.96). The mean positive likelihood ratio (LR+) was calculated at 14.53 (95% CI: 8.07 - 26.19), and the mean negative likelihood ratio (LR"), at 0.07 (95% CI: 0.05 - 0.09). Sakushima *et al*, in their systematic review, found that CSF lactate had LR+ of 22.9 (95% CI: 12.6 - 41.9), LR" of 0.07 (95% CI: 0.05 - 0.12), and diagnostic odds ratio of 313 (95% CI: 141 - 698). They concluded that the very low LR" indicated that lack of CSF lactate is particularly good for discarding BM[12]. Moreover, in the present study, there was a significant statistical difference in mean CSF lactate levels in different Glasgow outcome score patients. The mean CSF lactate was lower in patients with GOS-5 as compared to patients with GOS-1 with a p value of < 0.0001. It shows that CSF lactate levels had significant relationship with the prognosis of the patients, levels being less raised in patients with improved outcome and more raised in patients with worse outcome. Since the CSF lactate concentration is neither specific for BM nor for any specific bacteria in patients with BM, the results should always be interpreted in line with clinical findings and the results of conventional assays, including CSF concentrations of protein, cells, and glucose, as well as a microbiological CSF[18]. Furthermore, CSF lactate cannot be used for antibiotic selection, which must be based on the results of microscopic smear examination and/or culture for bacteria.

Studies in adults have indicated that adding CSF cortisol to routine CSF examination is better in estimating the chance of BM early[19]. In the present study, the mean CSF cortisol level in bacterial meningitis study population was 159.43 nmol/l with a Standard Deviation of 62.12, and the minimum and maximum values were 59.0 and 277.0 nmol/l respectively. Manjunath, BV (2015)[3] found out that mean cerebrospinal fluid cortisol activity was 13.06:g/dl, 4.44:g/dl, 2.29:g/dl and 1.05:g/dl in neutrophilic meningitis, lymphocytic meningitis, aseptic meningitis and controls respectively. Mean CSF cortisol level in neutrophilic meningitis was significantly higher as compared to other groups.

In the Holub *et al* study, the mean CSF cortisol was significantly elevated in neutrophilic meningitis (133 nmol/l) compared to aseptic (17 nmmo/l) and controls (10 nmol/l)[19], p value being signigicant (< 0.001).

There was a significant statistical difference in CSF cortisol levels in culture-positive bacterial meningitis and culture-negative bacterial meningitis. The mean CSF cortisol was lower in culture-positive bacterial meningitis (140.96 ± 48.38) as compared to culture-negative bacterial meningitis (170.35 ± 62.32) with a p value of 0.0429. This is in controversy to the study by Holub *et al*, in which it was observed that there was reverse significant difference in CSF cortisol levels in culture positive (162 nmol/l) and culture negative percent (103 nmol/l)[19]. In present study, there was no significant statistical difference in mean CSF cortisol levels in different Glasgow outcome score patients (p value 0.104). It shows that CSF cortisol levels had no significant relationship with the prognosis of the patients.

It can be concluded that a cut-off value of 3 mmol/l for CSF lactate and 50 nmol/l for CSF cortisol, had high diagnostic accuracy for BM but CSF lactate was found to be a better prognostic marker than CSF cortisol as patients with comparatively higher CSF lactate levels had severe neurological disability or died as compared to lower CSF lactate levels. This relationship was not seen in case of CSF cortisol. The present study had a number of limitations. Only a single measurement of lactate and cortisol was

made, upon hospital admission; repeat assessments to monitor treatment and response were not performed. Further, the results were not compared with conventional serum markers and CSF biomarkers (such as CRP).

## Conclusion

The present study indicated that for diagnosing BM, the CSF lactate concentration and CSF cortisol concentration are good independent indicators and better markers compared to other conventional markers including CSF glucose, CSF protein, and CSF total number of leukocytes. CSF lactate was found to be better prognostic marker than CSF cortisol in that it correlated with patients having adverse clinical outcome better than CSF cortisol. Cost effectiveness studies should be performed to investigate the economic impact of using this technique as a routine assay in hospital to diagnose BM.

## *References*


1. Roos KL. Bacterial Meningitis. *Curr Treat Ootions Neurol* 1999; 1: 147-56.
2. Tunkel AR, Hartman BJ, Kaplan SL *et al*. Practise guidelines for the management of bacterial meningitis. *Clin Infect Dis* 2004; 39: 1267-84.
3. Vishnuram P, Kumar N, Karuppusamy N *et al*. A Study on Estimation of Cortisol Levels in Cerebropinal Fluid for Differentiating Bacterial from Non Bacterical Meningitis. *IOSR J Dental Med Sci* (IOSR-JDMS); e-ISSN: 2279-0853, p-ISSN: 2279-0861. 2016; 15 (6 Ver. VII): PP-42.
4. Nazir M, Wani WA, Malik MA *et al*. Cerebrospinal fluid lactate: a differentialbiomarker for bacterial and viral meningitis in children. *J Pediatr (Rio J)* 2018; 94: 88-92.
5. Peltola H, Roine I. Improving the outcomes in children with bacterial meningitis. *Curr Opin Infect Dis* 2009; 22: 250-5.
6. Durand ML, Calderwood SB, Weber DJ *et al*. Acute bacterial meningitis in adults. A review of 493 episodes. *N Engl J Med* 1993; 328: 21-8.
7. Thomas KE, Hasbun R, Jekel J. The diagnostic accuracy of Kernig's sign, Brudzinski's sign, and nuchal rigidity in adults with suspected meningitis. *Clin Infect Dis* 2002; 35: 46-52.
8. Aronin SI, Peduzzi P, Quagliarello VJ. Community-acquired bacterial meningitis: risk stratification for adverse clinical outcome and effect of antibiotic timing. *Ann Intern Med* 1998; 129: 862-9.
9. van de Beek D, de Gans J, Spanjaard L *et al*. Clinical features and prognostic factors in adults with bacterial meningitis. *N Engl J Med* 2004; 351: 1849-59.
10. Berkley JA, Versteeg AC, Mwangi I *et al*. Indicators of acute bacterial meningitis in children at a rural Kenyan district hospital. *Pediatrics* 2004; 114: e713-9.
11. Waghdhare S, Kalantri A, Joshi R. Accuracy of physical signs for detecting meningitis: a hospital-based diagnostic accuracy study. *Clin Neurol Neurosurg* 2010; 112: 752-7.
12. Sakushima K, Hayashino Y, Kawaguchi T *et al*. Diagnostic accuracy of cerebrospinal fluid lactate for differentiating bacterial meningitis from aseptic meningitis: a meta-analysis. *J Infect* 2011; 62: 255-62.
13. Nigrovic LE, Kuppermann N, Macias CG *et al*. Clinical prediction rule for identifying children with cerebrospinal fluid pleocytosis at very low risk of bacterial meningitis. *JAMA* 2007; 297: 52-60.
14. Huy NT, Thao NT, Diep DT *et al*. Cerebrospinal fluid lactate concentration to distinguish bacterial from aseptic meningitis: a systemic review and metaanalysis. *Crit Care* 2010; 14: R240.
15. Menkes JH. The causes for low spinal fluid sugar in bacterial meningitis: another look. *Pediatrics* 1969; 44: 1-3.
16. Mekitarian Filho E, Horita SM, Gilio AE. Cerebrospinal fluid lactate level as a diagnostic biomarker for bacterial meningitis in children. *Int J Emerg Med* 2014; 7: 14.
17. Wenger JD, Hightower AW, Facklam RR *et al*. Bacterial meningitis in the United States, 1986: report of a multistate surveillance study. The Bacterial Meningitis Study Group. *J Infect Dis* 1990; 162: 1316-23.
18. Posner JB, Plum F. Independence of blood and cerebrospinal fluid lactate. *Arch Neurol* 1967; 16: 492-6.
19. Holub M, Beran O, Dzupova O *et al*. Cortisol levels in cerebrospinal fluid correlate with severity and bacterial origin of meningitis. *L Critical Care* 2007; 11: R41.