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# Performance of CSF Lactate for Diagnosis of Acute Bacterial Meningitis in Paediatric Population

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## Abstract

***Background:*** *Meningitis is a grave condition which demands prompt diagnosis and early treatment. Proper diagnosis needs identification of the causative agent. But isolation of organism is not always possible. Previous studies found that CSF lactate is increased in bacterial meningitis and its level does not alter immediately with treatment. So, CSF lactate can be used as an important marker to diagnose acute bacterial meningitis in children.* ***Methodology:*** *This cross-sectional study conducted at the department of Paediatrics in Dhaka Medical College and Hospital (DMCH), Dhaka, Bangladesh from September, 2018 to February, 2020. After initial screening of 132 suspected meningitis finally, 96 patients of acute meningitis were included in the study and divided into bacterial (n=34) and viral (n=62) meningitis groups based on the CSF results. CSF lactate in these two categories was analyzed. Based on the receiver-operator characteristic (ROC) curve, area under curve was identified for CSF lactate. Best cut off value along with sensitivity and specificity was calculated.* ***Results:*** *Among 96 patients, almost two third (64.6%) patients were diagnosed with viral meningitis and 34 (35.4%) with bacterial meningitis. Six (17.6%) patients were found blood culture positive in bacterial meningitis group. Twenty three (67.6%) patients were found with positive CSF gram staining and ten (29.4%) patients showed positive growth in CSF culture in bacterial meningitis group. The mean CSF lactate was 5.7±1.8mmol/L in bacterial meningitis group and 1.8±0.7 mmol/L in viral meningitis group. The difference was statistically significant (*p*<0.05) between two groups. Based on the receiver-operator characteristic (ROC) curves CSF lactate had area under curve 0.979. Best cut off value was calculated >2.2 mmol/L using Youden's Index with sensitivity 97.1%, specificity 87.1%.* ***Conclusion:*** *In this study CSF lactate >2.2 mmol/L was found highly sensitive and specific for diagnosis of acute bacterial meningitis in paediatric population.*


***Keywords:*** *Cerebrospinal Fluid (CSF), Lactate, Acute Bacterial Meningitis, Viral meningitis*

## Introduction:

Meningitis is the inflammation of covering of the brain and spinal cord. Fatality rates associated with meningitis can vary from as low as 2% in infants and children to as high as 20-30% in neonates and adults[1]. Complications like transient or permanent deafness or other neurological sequelae arise in up to 33% of survivors[2].

Common causes of neonatal bacterial meningitis are Group B streptococci (50-60%), *Escherichia coli* (15-20%) and other Gram negative organisms (10%). *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Hemophilus influenzae* type B are predominant causes of acute bacterial meningitis in the first year of life. Gram negative organism eg. *Escherichia coli,* Klebsiella spp, Enterobacter spp, Pseudomonas spp and *Hemophilus influenzae* type B can cause infection in immunocompromised patients[1]. *Streptococcus pneumoniae* is the commonest cause of acute


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bacterial meningitis in children. Approximately 70% of bacterial meningitis occur in children below 5 years of age[3].

Enterovirus is the most common cause of viral meningitis. Parechovirus is an important cause of aseptic meningitis or encephalitis in infants. Other causes of meningitis in children are Arbo virus, Herpes simplex type-1, Herpes simplex type-2, Varicella zoster, Cytomegalovirus, Mumps. Occasionally meningoencephalitis is caused by respiratory viruses (Adeno, Influenza, Parainfluenza, Rubeola or Rabies).

The case fatality rate in bacterial meningitis was 26% in developed countries even with antimicrobial therapy[4,5]. Permanent neurological sequel such as hearing loss, mental retardation, seizures and behavioral changes may occur in up to 50% of survivors[6]. Because of the high mortality and morbidity resulting from bacterial meningitis, rapid and accurate diagnosis followed by prompt treatment is needed to increase the survival rate and to reduce complications.

Laboratory support is essential for rapid diagnosis of meningitis[4]. Conventional methods of diagnosis of bacterial meningitis is based on examination of CSF including physical, biochemical, cytological, Gram staining and culture[7]. The gold standard for diagnosis of any infection including meningitis is the isolation and identification of the causative agent[8].

In Gram staining, concentrations less than $10^3$ CFU per ml of CSF are associated with positive findings in only 25%[9]. Widespread use of antibiotics before during CSF cultures make difficult to interpret the results because CSF cultures may be negative within hours of antibiotic administration[10]. It also take time for bacterial growth and may give false results if not properly transported and stored as they are fastidious organism[7].

Measurement of CSF Lactate concentration was found effective to differentiate bacterial from viral meningitis in previous studies[10]. CSF lactate is produced by anaerobic metabolism and the level increases in any condition which causes decrease in oxygen supply to the brain and there is no correlation with serum lactate level[11]. The CSF lactate level of 3.5mmol/l or greater has been considered by some authors superior to the other CSF test to diagnose and differentiate bacterial meningitis from viral meningitis[12].

The CSF parameters, Gram staining and culture results still remains the most useful method of diagnosis of meningitis, but the patients in whom the CSF Gram stain and culture results are negative there is no test that is definitive for or against the diagnosis of bacterial meningitis. Recently several studies found CSF lactate to be useful for diagnosis of bacterial meningitis. The purpose of this study was to see the role of CSF lactate to diagnose acute bacterial meningitis.

**Methods:**

This cross sectional study was conducted from September, 2018 to February, 2020 in the Department of Paediatrics of Dhaka Medical College and Hospital (DMCH), Dhaka, Bangladesh.

Patients of suspected acute meningitis in children admitted in department of paediatrics, DMCH, Dhaka were selected as study population. Purposive sampling was done. Patients already getting antibiotic for acute meningitis and suspected cases of tubercular and fungal meningitis were excluded from the study. Data were collected through predesigned data collection sheet.

A total of 132 children admitted into the Paediatric ward, having the clinical features of acute meningitis, were evaluated. History taking and through physical examination were done and findings were recorded on a structured form. Informed written consent was taken from patient's guardian. Blood samples for necessary laboratory investigations including CBC, CRP, blood sugar, serum electrolyte and serum calcium and culture/ sensitivity were collected. Lumber puncture was done to every patient before commencing antimicrobial therapy. Two ml (30 drops) of CSF was collected by lumber puncture into two clear, sterile tubes. One ml CSF was collected in one tube for cytology, total protein, glucose and lactate level, while another ml was taken in a different tube for Gram stain, culture sensitivity and AFB stain. CSF lactate level was measured by enzymatic

colorimetric method by Siemens Dimension EXL LM. Finally, 96 patients who met the criteria of operational definition of acute bacterial and viral meningitis were included in the study and were divided into bacterial and viral meningitis groups. CSF lactate in these two groups was analyzed and a best cutoff value along with its sensitivity and specificity was calculated.

The collected data of each patient was recorded systematically. All data were analyzed by using computer-based SPSS 23 (statistical package for social sciences). Data were presented in frequency, percentage and mean and standard deviation as applicable. Chi square test was used for categorical variables. Unpaired t-test was used for continuous variables. Based on the receiver-operator characteristic (ROC) curves, area under curve was identified for CSF lactate. P value of less than 0.05 was considered significant.

**Results:**

**Table-I**

*Distribution of the study patients by diagnosis (n=96)*

| Diagnosis | Number of patients | Percentage (%) |
|---|---|---|
| Bacterial meningitis | 34 | 35 |
| Viral meningitis | 62 | 65 |

**Table II**

*Distribution of the bacterial and viral meningitis patients according to demographic variables (n=96)*

| Socio-demographic | Bacterial(n=34) | | Viral(n=62) | | *p* value |
|---|---|---|---|---|---|
| Variables | n | % | n | % | |
| Age (years) | | | | | |
| <1 | 13 | 38 | 15 | 24 | |
| 1-5 | 6 | 18 | 17 | 28 | [a]0.294[ns] |
| >5 | 15 | 44 | 30 | 48 | |
| Sex | | | | | |
| Male | 15 | 44 | 40 | 64 | [a]0.053[ns] |
| Female | 19 | 56 | 22 | 36 | |
| Mean±SD | Mean±SD | | | | |
| Z score (age ≤5 years) | -1.12±0.58 | | -0.84±0.60 | | [b]0.113[ns] |
| BMI (kg/m$^2$) (age >5 years) | 16.5±0.8 | | 16.2±1.5 | | [b]0.429[ns] |

ns= not significant
[a]P value reached from chi square test
[b]P value reached from unpaired t-test

**Table-III**

*Distribution of the bacterial and viral meningitis patients according to blood culture (n=96)*

| | Bacterial (n=34) | | Viral (n=62) | | *p* value |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Blood culture | | | | | |
| No growth | 28 | 82 | 62 | 100 | 0.012[s] |
| Growth | 6 | 18 | 0 | 00 | |
| *S. pneumoniae* | 2 | 6 | 0 | 00 | |
| *E. coli* | 1 | 3 | 0 | 00 | |
| Enterococcus | 1 | 3 | 0 | 00 | |
| Pseudomonas | 1 | 3 | 0 | 00 | |
| Acinetobacter | 1 | 3 | 0 | 00 | |

s= significant
*p* value reached from chi square test

Table III shows that 6(17.6%) patients were found blood culture positive in bacterial meningitis group. The difference was statistically significant ($p<0.05$) between two groups.

**Table-IV**

*Distribution of the bacterial and viral meningitis patients according to CSF Gram staining and Culture (n=96)*

| | Bacterial (n=34) | | Viral (n=62) | | *p* value |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Gram staining | | | | | |
| Positive | 23 | 68 | 0 | 00 | [a]0.001[s] |
| Negative | 11 | 32 | 62 | 100 | |
| Culture | | | | | |
| No growth | 24 | 71 | 62 | 100 | [a]0.001[s] |
| Growth | 10 | 29 | 0 | 00 | |
| *Strep. pneumonie* | 5 | 15 | 0 | 00 | |
| *N. meningitides* | 2 | 6 | 0 | 00 | |
| *E. coli* | 2 | 6 | 0 | 00 | |
| Staphylococcus | 1 | 3 | 0 | 00 | |

s= significant, ns= not significant
*p* value reached from chi square test

Table IV shows that 23(67.6%) patients were found with positive CSF gram staining and 10(29.4%) patients showed positive growth in CSF culture in bacterial meningitis group. The differences were statistically significant ($p<0.05$) between two groups.

**Table-V**

*Distribution of the bacterial and viral meningitis patients according to CSF Lactate (n=96)*

| | Bacterial(n=34) Mean±SD | Viral(n=62) Mean±SD | *p* value |
|---|---|---|---|
| CSF lactate (mmol/L) | 5.7±1.8 | 1.8±0.7 | 0.001[s] |
| Range (min-max) | 1.8-9.1 | 1.1-4.3 | |

s= significant
*p* value reached from unpaired t-test

Table V shows that mean CSF lactate was 5.7±1.8mmol/L in bacterial meningitis group and 1.8±0.7 mmol/L in viral meningitis group. The difference was statistically significant ($p<0.05$) between two groups.
Fig.-1: Receiver-operator characteristic curves of CSF lactate level
Figure 1 shows that receiver-operator characteristic (ROC) curve of CSF lactate had area under the curve (AUC) 0.979.

**Table-VI**

*Evaluation of CSF Lactate for diagnosis of acute bacterial meningitis (n=96)*

| CSF lactate (mmol/L) | CSF culture | | Total |
|---|---|---|---|
| | Positive | Negative | |
| ≥2.2 | 9(True positive) | 23(False positive) | 32 |
| <2.2 | 1(False negative) | 63(True negative) | 64 |
| Total | 10 | 86 | 96 |

CSF lactate level ≥2.2 mmol/L for diagnosis of acute bacterial meningitis showed true positive 9 cases, false positive 23 cases, false negative 1 case and true negative 63 cases in identification by CSF culture.

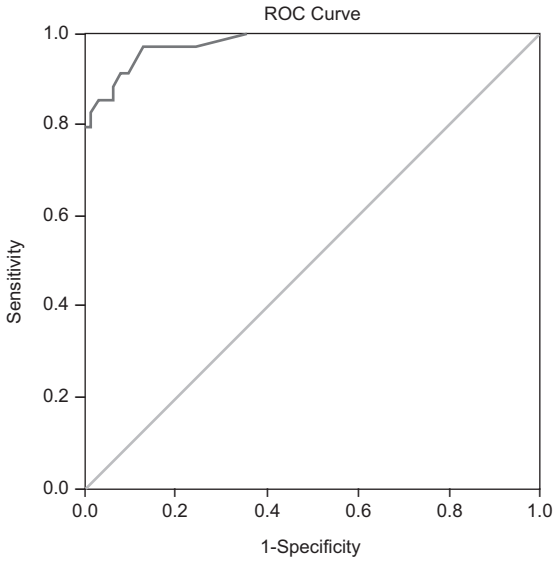


**Fig.-1:** *Receiver-operator characteristic curves of CSF lactate level*

Figure 1 shows that receiver-operator characteristic (ROC) curve of CSF lactate had area under the curve (AUC) 0.979.

**Discussion:**

This study aimed to find the role of CSF lactate level to diagnose acute bacterial meningitis in children where 34(35.4%) patients were diagnosed as a case of acute bacterial meningitis. Study conducted by van Anh et al.[13]had the similar observation where out of 54 pediatric acute meningitis patients, 23(42.6%) were bacterial and 31(57.4%) were viral meningitis. Nazir et al.[14] also found similar results.

In this present study, we didn't find any significant difference regarding age of onset between two groups but Nazir et al.[14] found that the mean age of patients in bacterial meningitis group was significantly lower than those in viral meningitis group. There was no significant difference in gender distribution in this study which finding is consistent with the findings of Nazir et al.[14] and Filho et al.[15].

From the 6(17%) blood culture positive cases of bacterial meningitis group the identified organisms were *S. pneumonia* (2), *E. coli* (1), Enterococcus (1), Pseudomonas (1), Acinetobacter (1). Results of culture positivity reported by Nazir et al.[14] and Abro et al.[16] was 9(15%) and 15 (28.3%) patients respectively.

CSF Gram staining and culture have shown more sensitivity compared to blood culture in this study where we found 23 patients had positive CSF Gram staining and 10 patients had growth in CSF culture in bacterial meningitis group and the identified organisms were *Strepto. pneumonie* (5), *N. meningitidis* (2), *E. coli* (2) and Staphylococcus (1). Five patients were also found positive on both CSF gram staining and culture. Nazir et al.[14] found quite similar findings where gram-staining was positive in 16 (26.7%) patients and CSF culture was positive in 19(31.7%) patients in bacterial meningitis group. This result is differing with a study conducted in Bangladesh where 587(69%) were detected culture positive out of 852 cases[3].

Though the mechanism of the raised CSF lactate in meningitis patient is still unclear but it is thought to be linked with the anaerobic glycolysis of brain tissue due to reduced blood flow and oxygen uptake which found significantly increased in bacterial meningitis group compared to viral meningitis group (5.7±1.8vs1.8±0.7 mmol/L) and this findings were also observed by van Anh et al.[13]; Nazir et al.[14] and Abro et al.[16].

It was observed in this study that based on the receiver-operator characteristic (ROC) curve, CSF lactate had area under curve 0.979. Best cut off value was mathematically calculated using Youden's Index which gave a best cut off value >2.2mmol/L, with 97.1% sensitivity and 87.1% specificity for prediction of acute bacterial meningitis. Van Anh et al.[13]; Nazir et al.[14] and Filho et al.[15] found AUC for CSF Lactate was 0.87, 0.979 and 0.96 respectively. CSF lactate level e"3.0 mmol/l had a sensitivity of 87.0%, 90% and 95%, specificity of 87.1%, 100% and 93.6% respectively in those 3 studies. None of them used Youden's Index to calculate best cut-off value. Two recent meta-analyses evaluated the ability of CSF lactate to distinguish aseptic from bacterial meningitis[17,18]. Using a CSF lactate cutoff point between 2.1 and 4.4 mmol/l, the aggregated sensitivity of CSF lactate for bacterial meningitis was 93% or 96% and specificity 94% or 96%, respectively.

**Conclusion:**

In this study CSF lactate >2.2mmol/L was found highly sensitive and specific to differentiate bacterial meningitis from viral meningitis as the sensitivity of culture positivity is less due to early use of antibiotics. So CSF lactate can be a cost effective diagnostic markers for bacterial meningitis. Further large scale multicenter study with large sample size is required to generalize the results.

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