

# Utility of Urine Reagent Strips for Analysis of Cerebrospinal Fluid in Emergency Settings: A Cross-sectional Study

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## ABSTRACT

**Introduction:** Meningitis is the inflammation of the meninges which covers brain and spinal cord, which if not identified on time will result in permanent neurological deficit or death. Mainly divided into septic and aseptic meningitis, differentiating these two and timely intervention would prevent neurological damage. Cerebrospinal Fluid (CSF) analysis helps to arrive at a diagnosis of meningitis which requires relevant trained staff and adequately equipped laboratory. These are not available in most of the healthcare centers in rural settings.

**Aim:** To evaluate the role of urinary reagent strip method in rapid analysis of CSF, to assist the clinician in the bedside diagnosis or exclusion of meningitis and to compare the values obtained by rapid method with that of results obtained by automated analyser.

**Materials and Methods:** This cross-sectional study was done in Pathology laboratory of Mandya Institute of Medical Sciences,

District Hospital, Karnataka, Mandya, India. A total of 30 samples evaluated during the period of two months in 2019 (15<sup>th</sup> August to 15<sup>th</sup> October). Cerebrospinal fluid analysis was tested using combur- 10 urinary reagent strip and microscopy examination as reference standards. Automated analysers were used for the analysis of protein and glucose; and Neubauer's counting chamber was used for leucocytes count. Statistical Package for the Social Science (SPSS) version 22.0 and Microsoft Excel were used to analyse data and generate tables.

**Results:** The sensitivity and specificity of urinary strips in the analysis of cerebrospinal fluid for glucose, protein, leucocytes was 50.00%, 41.67%, 78.57% and 92.31%, 88.89%, 68.75% respectively. Diagnostic accuracy of urinary strip tests for glucose, protein and leucocytes were 83.33% 93.34% 86.67% respectively.

**Conclusion:** The study shows the reliable sensitivity and specificity in some parameters, hence can be used in remote settings.

**Keywords:** Automated analyser, Bacterial meningitis, Dirui urinary reagent strips, Lumbar puncture, Medical emergency

## INTRODUCTION

Cerebrospinal Fluid (CSF) flows in subarachnoid space that lies between arachnoid and pia mater [1]. The production of CSF is from choroid plexus and lateral ventricles [2]. The main functions of CSF include a) mechanical protection to brain from physical shocks; b) chemical protection and regulatory function to create a buffer for optimal neuronal signalling; c) circulation and exchange of nutrients and waste and; d) excretory of brain metabolites [3,4].

Meningitis is the inflammation of meninges. The causative agents include bacterial, viral, fungal and parasitic infections [5]. If meningitis is not identified rapidly, it can result in permanent neurological damage or even death [6]. Globally, bacterial meningitis is the leading cause of mortality among children under five years of age [7]. Viral meningitis is also known as aseptic meningitis which is less severe and requires only symptomatic treatment. Cerebrospinal fluid analysis helps to arrive at a diagnosis of meningitis for timely medical intervention.

Healthcare personnel with relevant training and adequately equipped laboratory are required for the analysis of cerebrospinal fluid which are not available in most healthcare centres in rural settings [8]. In such areas, a rapid test which can help in quick diagnosis will be very useful. Current diagnosis methods are time consuming and expensive. As meningitis is a medical emergency, rapid diagnosis is very important to initiate necessary treatment and reduce morbidity and mortality [9]. Urinary reagent strips have been used previously as a rapid diagnostic test in diagnosis of meningitis. However, there have been variations in correlation between standard biochemical methods and outcome of urinary reagent method and also there are no well-defined cut-off values defines for urinary reagent strip method to establish diagnosis of meningitis [10].

Several studies were carried out on the role of urinary reagent strips with different outcomes. A study done by Akram D and Shaikkh AM

for the rapid evaluation of cerebrospinal fluid analysis in remote areas by use of glucometer works as cost-effective tool and rapid results [11]. Omar M et al., have proposed the use of the urinary strip reagent in evaluation of synovial fluid for septic arthritis for leucocytes and glucose. It has got high sensitivity and specificity which can be utilised for diagnosing septic arthritis [12]. A similar study was done by Koulaouzidis A for the diagnosis of bacterial peritonitis using the leucocyte esterase strips [13]. Joshi D et al., showed that urinary reagent strips can reliably predict raised CSF protein (>100 mg/dL), decreased glucose (<40 mg/dL), and increased neutrophil count (>10/mm<sup>3</sup>). These strips can therefore be relied upon to make a rapid diagnosis of meningitis and initiate appropriate treatment, particularly in areas with limited resources [14].

The present study intends to evaluate the usefulness of urinary strip method and correlate its values with the standard biochemical test. An attempt has also been made to define cut-off values which will have high specificity for diagnosing meningitis. This method will help clinicians to quickly arrive at a diagnosis and initiate timely intervention.

### Study Objectives:

- To evaluate the role of urinary strip reagent method in the analysis of CSF to assist clinicians in bedside diagnosis or exclusion of meningitis.
- To compare the values obtained by rapid method with that of results obtained by automated analyser.

## MATERIALS AND METHODS

A cross-sectional study was carried out in 30 CSF samples over a period of two months in 2019 (15<sup>th</sup> August-15<sup>th</sup> October). CSF samples from patients of any age group who had an indication for lumbar puncture like fever, headache, intractable vomiting, altered sensorium, neurological deficit, irritability, behavioural changes, seizures and meningeal signs like neck stiffness, Kernig's sign,

Budzinski's sign were included. The samples were received within one hour of tap from lumbar puncture. The study did not involve any additional risk to the participants as samples collected for routine diagnosis were used for the present study. No additional invasive procedure was therefore required to collect samples. The study proposal was submitted to Institutional Ethics Committee (IEC) and approval was obtained.

#### Inclusion criteria:

1. CSF samples received within one hour of lumbar puncture tap.
2. Sample volume  $\geq 0.5$  mL

#### Exclusion criteria:

1. Haemorrhagic taps
2. Samples received after one hour of tap
3. Inadequate samples  $< 0.5$  mL

#### Index Test

Followed by the dirui urinary reagent strips which can detect parameters like protein, glucose and leucocyte esterase activity in the urine were utilised for this test. This was done by an independent blind investigator. The test was performed by adding few drops of undiluted CSF fluid to the respective patches on the urinary reagent and colour change will be noted. The colour change was then matched with colour coding provided by the manufacturer and the results were recorded and interpreted as in [Table/Fig-1].

Depending on the colour changes, leucocytes are graded as per the values provided by the dirui company. The reagent strip-based colour changes observation for protein as per the values provided by the dirui company [Table/Fig-2].

Result	Cell count
Negative	$< 15$ cells/cumm
1+	$\geq 15-70$ cells/cumm
2+	$> 70-125$ cells/cumm
3+	$> 125-500$ cells/cumm

[Table/Fig-1]: Grading of leucocytes for cell count.

Result	Protein
Negative	$< 15$ mg/dL
1+	$> 15-30$ mg/dL
2+	$> 30-100$ mg/dL
3+	$> 100-300$ mg/dL
4+	$> 300-2000$ mg/dL

[Table/Fig-2]: Grading of protein.

The normal level of CSF glucose is  $2/3^{\text{rd}}$  of the plasma level. Very low levels of glucose are seen in bacterial meningitis. Using the determined strip, if the values were above or below 50 mg/dL with the interpretation being no change in colour as  $< 50$  mg/dL and any change in colour as  $> 50$  mg/dL [Table/Fig-3].

Result	Glucose
Negative	$\leq 100$ mg/dL
1+	$> 100-250$ mg/dL
2+	$> 250-500$ mg/dL
3+	$> 500-1000$ mg/dL
4+	$> 1000-2000$ mg/dL

[Table/Fig-3]: Grading of glucose.

The reagent strip-based colour changes observation for glucose as per the values provided by the dirui company.

#### Definitive Test

Total leucocyte count was carried out by Neubauer's counting chamber, by charging with undiluted CSF sample, which is followed

by differential count done from the smears prepared from centrifuged sediment smear stained with May-Grunwald-Giemsa (MGG) stain. The results were recorded and interpreted.

The CSF samples were processed and analysed in abott automated analyser for protein and glucose. The results are recorded and interpreted. The standard reference values of Neubauer's chamber and abott automated ranges from 0-5 cells/cumm and Protein-15-45 mg/dL; Glucose-45-80 mg/dL respectively.

#### STATISTICAL ANALYSIS

The accuracy of the reagent strip was estimated using standard statistical tests and tabulated in the form of sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) and Positive and Negative Likelihood Ratios (PLR and NLR). Statistical Package for the Social Science (SPSS) version 22.0 and Microsoft Excel were used to analyse data and generate tables.

#### RESULTS

The study was conducted on 30 CSF samples. Majority of the samples received were from patients in the age group of 30-60 years. Males and females represented 20 (66.67%) and 10 (33.33%) of samples respectively.

Three parameters were studied for analysis of CSF i.e., glucose, proteins, and leucocytes using the urinary strip. The values were correlated with reference standard values, i.e., for cell count-Neubauer's chamber; protein and glucose-Abott automated instrument. In the present study, dirui urinary strips used for the analysis of cerebrospinal fluid. The strip had a moderate sensitivity and specificity for leucocytes  $\geq 15$  cells/cumm. With respect to proteins, the results are acceptable for a higher cut-off level of  $\geq 100$  mg/dL [Table/Fig-4].

	Glucose	Protein	Leucocytes
Sensitivity	50.00%	41.67%	78.57%
Specificity	92.31%	88.89%	68.75%
PPV	50.00%	71.43%	68.75%
NPV	92.31%	69.57%	78.57%
PLR	2.75%	3.41%	2.43%
NLR	0.76%	0.67%	0.32%
Accuracy	83.33%	93.34%	86.67%

[Table/Fig-4]: Diagnostic accuracy of urinary strip tests for analysing glucose, protein and leucocytes.

**Leucocytes:** Leucocytes were detected by the esterase activity. The sensitivity and specificity for leucocytes by the strip method for  $> 15$  cells/cumm showed moderate sensitivity and specificity of 78.57% and 68.75%, respectively. The PPV, NPV, PLR, NLR and accuracy showed to be 68.75%, 78.57%, 2.43%, 0.32% and 86.67%, respectively.

**Proteins:** The reagent strip had a sensitivity and specificity of 41.67% and 88.89%, respectively. This shows sensitivity towards proteins is very low compared to specificity. The PPV, NPV, PLR, NLR and accuracy showed to be 71.43%, 69.57%, 3.41%, 0.67% and 93.34%, respectively.

**Glucose:** Glucose was detected in CSF by glucose oxidase-peroxidase method. The reagent strip test for glucose had a sensitivity and specificity of 50.00% and 92.31%, respectively. This study for glucose also showed low sensitivity and high specificity. The PPV, NPV, PLR, NLR and accuracy showed to be 50.00%, 92.31%, 2.75%, 0.76% and 83.33%, respectively.

#### DISCUSSION

Meningitis is an emergency medical condition which has a high mortality rate. In order to prevent the postneurological consequences, antibiotics have to be started within three hours. Cerebrospinal fluid

analysis has to be done within one hour of tap and it should not be refrigerated and delayed as it causes autolysis of the leucocytes and gives a false negative result. More recently, liberal use of antibiotics has led to emergence of the resistant strains that cause meningitis. Abdelmotalieb GS et al., showed leucocyte sensitivity and specificity at cut-off >10 cells as 100% and 75% respectively [15]. Gupta A and Dwivedi T by use of cut-off  $\geq 10$  cells/cumm and confidence interval of 95% for leucocytes, the sensitivity and specificity as 100% and 96.3%, respectively [16]. Bhat A et al., showed sensitivity and specificity by use of strip test as 36.36% and 85.71% respectively by using cut-off >10 cells/cumm [10]. Rajkumar D et al., with the use of confidence interval of 95% showed that the sensitivity and specificity of leucocytes as 90% and 91.67%, respectively for diagnosis of meningitis [17]. Sharma D and Uradiya I study group showed that leucocyte sensitivity and specificity at as 94% and 98.5%, respectively at a cut-off >10 cells [18]. This study also showed

almost same results for leucocytes as Bhat A et al., with sensitivity and specificity being 78.57% and 68.75%, respectively [10]. This study is in contrast with these studies [Table/Fig-5] [8,10,15-18].

Abdelmotalieb GS et al., showed protein reagent strip sensitivity and specificity as 100% and 50% respectively at a cut-off 100 mg/dL [15]. Gupta A and Dwivedi T showed sensitivity of 98.9% and low specificity of 54.2% with confidence interval of 95% [16]. Bhat A et al., showed sensitivity of 100% and very low specificity of 28.57% with the use of cut-off >30 mg/dL [10]. Rajkumar D et al., showed a sensitivity and specificity for protein with confidence interval of 95% as 93.20% and 91.49%, respectively [17]. Sharma D and Uradiya I study showed protein reagent strip sensitivity and specificity as 100% and 50%, respectively and with accuracy of 99% [18]. The present study showed sensitivity of 41.67% which is in contrast to other studies and specificity of 88.89% which is similar to that of other studies.

	Present study	Abdelmotalieb GS et al., [15]	Gupta A and Dwivedi T [16]	Bhat A et al., [10]	Rajkumar D et al., [17]	Sharma D and Uradiya I [18]	Chikkannaiah P et al., [8]
<b>Sensitivity</b>							
Leucocytes >10 cells/cumm	78.57%	100.00%	100%	36.36%	90%	94.0%	96.6%
Protein >30 mg/dL >100mg/dl	41.67%	100%	98.9%	100%	93.20%	100% 93%	94.9% 96.0%
Glucose >50 mg/dL	50.00%	96.8%	98.1%	-	90%	98.5%	28.5%
<b>Specificity</b>							
Leucocytes >10 cells/cumm	68.75%	75.00%	96.3%	85.71%	91.67%	98.5%	94.5%
Protein >30 mg/dL >100 mg/dL	88.89%	50%	54.2%	28.57%	91.49%	50% 98.5%	45.8% 87.1%
Glucose >50 mg/dL	92.31%	100%	92.3%	-	91.67%	100%	100% 100%
<b>PPV</b>							
Leucocytes >10 cells/cumm	68.75%	-	-	-	94.19%	-	87.8%
Protein >30 mg/dL >100 mg/dL	71.43%	-	-	-	96%	-	85.2%
Glucose >50 mg/dL	50.00%	-	-	-	94.19%	-	100% 100%
<b>NPV</b>							
Leucocytes >10 cells/cumm	78.57%	-	-	-	85.94%	-	98.5%
Protein >30 mg/dL >100 mg/dL	69.57%	-	-	-	86%	-	73.3%
Glucose >50 mg/dL	92.31%	-	-	-	85.94%	-	89.2% 75.7%
<b>PLR</b>							
Leucocytes 10 cells/cumm	2.43%	-	-	-	-	-	17.64%
Protein >30 mg/dL >100 mg/dL	3.41%	-	-	-	-	-	1.75%
Glucose >50 mg/dL	2.75%	-	-	-	-	-	Infinity
<b>NLR</b>							
Leucocytes >10 cells/cumm	0.32%	-	-	-	-	-	0.035%
Protein >30 mg/dL >100 mg/dL	0.67%	-	-	-	-	-	0.11%
Glucose >50 mg/dL	0.76%	-	-	-	-	-	0.714%
<b>Accuracy</b>							
Leucocytes >10 cells/cumm	86.67%	97%	-	-	90.67%	97%	-
Protein >30 mg/dL >100 mg/dL	93.34%	99% 97%	-	-	92.67%	99% 97%	-
Glucose >50 mg/dL	83.33%	99.0%	-	-	90.67%	99.0%	-

[Table/Fig-5]: Comparison of diagnostic accuracy with other studies [8,10,15-18].

Abdelmotalieb GS et al., showed glucose reagent strip sensitivity and specificity as 96.8% and 100% at cut-off 46 mg/dL [15]. Gupta A and Dwivedi T showed with the use of confidence interval of 95%, sensitivity and specificity as 98.1% and 92.3%, respectively [16]. Sharma D and Uradiya I Glucose reagent strip sensitivity and specificity as 98.5% and 100% at cut-off 50 mg/dL and with accuracy of 99% [19]. Rajkumar D et al., showed sensitivity and specificity of 90.00% and 91.67%, respectively with confidence interval of 95% [17]. The present study showed very low sensitivity for glucose which is in contrast to other studies but specificity of 92.31% which is similar to other studies.

Sharma D and Uradiya I showed the accuracy for leucocytes, protein and glucose as 97%, 99% and 99%, respectively [18]. Rajkumar D et al., showed that the accuracy for the leucocytes, protein and glucose as 90.67%, 92.675 and 90.67%, respectively [17]. The present study showed accuracy for leucocytes, protein and glucose as slight similar to that of other studies as 86.67%, 93.34% and 83.33%, respectively. Abdelmotalieb GS et al., mention that use of this urinary strip reagent in diagnosis of meningitis is a qualitative or semi-quantitative method. It does not give an accurate result and it should not be taken as final test result, the result obtained can be used to make a decision, whether to start antibiotics immediately or not [15].

In the present study, the leucocytes sensitivity and specificity by strip method were 78.57% and 68.75%, respectively. The reagent strip is highly specific for glucose and protein (92.31%, 94.12%, respectively) but is less sensitive (50.00%, 53.85%, respectively). The reagent strip is moderately specific and sensitive for leucocytes. The strips are highly specific for the estimation of glucose and protein and moderately specific for leucocytes estimation, but they are low sensitive for estimation of glucose and protein but moderately sensitive for leucocytes estimation.

The protein and glucose tests by urinary strip were found to be reliable and can be used as screening test for the diagnosis. It also helps the clinician suspecting meningitis in remote areas to decide whether to administer antibiotics or not. The leucocytes test by urinary strip test, showed to be less helpful in the diagnosis, as it had showed more false positive results compared to the values obtained through the Neubauer's chamber. This method, therefore, cannot be used as a substitute to standard automated analysers and Neubauer's chamber. The results obtained in the present study did not fully correspond to the standard method.

### Limitation(s)

The major drawback of the present study is the small sample size compared to other studies. The present study results may have differed because of the use of different method of urinary strips, that might have affected sensitivity and specificity. Standardising

this method by using a particular type/make of strips, may help in validating this method.

### CONCLUSION(S)

Based on the results of these studies, it was concluded that urinary strip reagent can be utilised for analysis of cerebrospinal fluid as it has got reliable sensitivity and specificity. Though, the present study results did not fully correlate with other studies, this method may still be utilised as a tool in remote areas where automated analysers are unavailable to guide in clinical decision making.

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