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Original Research Article

A study of cerebrospinal fluid C-reactive protein in bacterial meningitis among paediatric age group in a tertiary care hospital

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ABSTRACT

Background: Bacterial meningitis is a significant cause of mortality and morbidity in children worldwide. C-reactive protein (CRP) raises rapidly in the first 24-48 hours of occurrence of bacterial meningitis and in large incremental increases thereafter. The present study was undertaken to find out the correlation between cerebrospinal fluid (CSF)-CRP and bacterial meningitis in paediatric age group.
Methods: A total 123 children aged between 1 month to 12 years, in whom meningitis was suspected during the study period were included. Lumbar puncture performed at L3-L4 and CSF sample not more than 3 ml collected in 4 sterile containers. 1ml sent for protein and sugar, 0.5ml each sent for CSF cytology and CSF-CRP, 1ml sent for CSF culture sensitivity and gram staining.
Results: The institutional incidence of bacterial meningitis was 3.37%. Fever (93.26%) and altered sensorium (92.30%), were the commonest symptoms and neck rigidity (58.65%) was the commonest meningeal sign. The neurologic assessment showed abnormal mental status (34.61%), abnormal cranial nerve findings (10.57%) and abnormal motor function (13.46%). The mean CRP level was 15.36±0.67 mg/l. Pneumococcus was the commonest isolated organism (53.48%) in CSF culture. The institutional mortality was 13.46%. CSF-CRP was positive in 104 (82.69%) of the culture-positive cases with a sensitivity of 82.69%, specificity 84.21%, positive predictive value 96.62% and negative predictive value of 47.05%.
Conclusions: CRP levels in CSF offers a moderate sensitivity and specificity as well as high positive predictive value. This indicates that CSF-CRP is a better marker in differentiating bacterial meningitis and it can serve as a useful screening test for bacterial meningitis.

Keywords: Bacterial meningitis, C-reactive protein, Cerebrospinal fluid

INTRODUCTION

Meningitis is defined as an inflammatory condition involving the membranes (meninges) covering the brain and spinal cord. It can have infectious causes, such as bacteria, mycobacteria, viruses, fungi, or parasites, or be associated with autoimmunity, cancer, or reactions to medication.[1] Meningitis continues to be a formidable illness with high morbidity and mortality in India. Gram positive cocci and gram-negative bacilli have been incriminated as bacterial aetiological agents of pyogenic meningitis in various studies.[2,3] Bacterial meningitis is a life-threatening illness. Early recognition and appropriate antibiotic treatment is crucial to reduce morbidity and mortality.

The diagnosis of bacterial meningitis poses the biggest challenge as the clinical and biochemical picture is often masked because of prior improper antibiotic usage. This becomes even more difficult in a population who are first catered usually by private practitioners and receive antibiotic course before confirming diagnosis. They are

then referred to tertiary care hospital in the due course. In such a scenario, the isolation of the organisms from blood or CSF becomes very difficult.[4] In a developing country like India, facilities to appropriately isolate blood- or CSF-borne organisms are scarce and even if available culture reports are usually time consuming. Moreover, CSF cultures for pyogenic organisms are positive in only 30–60% of cases, according to various researchers.[5] The lack of a single test to diagnose the aetiology of meningitis promptly and accurately, makes it more important to find a quick and reliable method for early bedside diagnosis.

CSF-CRP is a test which meets all this criterion, unlike CSF cytology and biochemistry does not require a lot of knowledge and skills and equipment's to interpret the results.[6] Hence, the present study was undertaken to evaluate the diagnostic significance of CRP in CSF as an early indicator in the differentiation of bacterial from non-bacterial meningitis.

METHODS

After obtaining institutional ethical committee approval, this hospital based observational study was conducted in the paediatric ward of tertiary care hospital in central India over a period of 1 year from 01 of January 2021 to 31 December 2021. A total 123 children aged between 1 month to 12 years, in whom meningitis was suspected during the study period with any of the following clinical criteria suggestive of CNS infection.

Signs of meningeal irritation like neck rigidity, Kernig sign positive, and Brudzinski sign positive.

Signs of raised Intra cranial tension like vomiting, headache, cranial nerve involvement, bulging anterior fontanelle, and Cushing's triad. Signs of encephalopathy, like convulsions, lethargy, irritability, coma, altered sensorium, behavioural disturbances, and any other neurological deficit.

Diagnosed case of TB meningitis, children with known immune function disorder, known case of intracranial malformation, patients who were discharged against medical advice, who were referred to higher centre and failure to obtain CSF sample even after 3 attempts were excluded from the study.

Assent of the child was also obtained verbally if the child is more than 7 years of age as per ICMR guidelines. Simultaneously socio-demographic data (age and sex), clinical history, physical examination of each patient was done, and management initiated based on provisional diagnosis. Lumbar puncture performed as per protocol after obtaining informed consent for the same. Under strict aseptic precaution, patient in knee chest position/flexion position and care was taken not to obstruct airway. Lumbar puncture performed at L3- L4 after properly painting and draping the prescribed area. Appropriately sized lumbar puncture needle was used to do the procedure (1.5 for <1 year, 2.5 for 1 year to middle childhood, 3.5 for older children). If LP was unsuccessful at the L3- L4 level, one level above was tried, and a maximum of three attempts were done. If CSF is not obtained even after 3 attempts, then the patient was excluded from study. CSF sample not more than 3 ml collected in 4 sterile containers and 1 ml sent for protein and sugar, 0.5 ml each sent for CSF cytology and CSF CRP, 1 ml sent for CSF culture sensitivity and gram staining.

C-reactive protein was measured in CSF by latex agglutination method using RHELEX-CRP® manufactured by Coral clinical systems company based on Uttarakhand. CRP levels more than 6 mg/dl is considered positive in this qualitative study. CSF culture and Gram stain, cytology and biochemical analysis were used as confirmatory markers. CSF- CRP was compared against these established parameters. Final diagnosis of the patients was considered based on the below stated working diagnosis-

Pyogenic meningitis

Among the clinically suspected cases of meningitis, irrespective of other parameters, CSF culture positivity marks the diagnosis of bacterial meningitis. Since cerebrospinal fluid culture for pyogenic organisms is positive, only in 30-60% of cases according to various Indian studies.[10,11]

Culture negative cases were considered as pyogenic meningitis if the other CSF parameters cellularity – leukocytes >10 with neutrophilic predominance >20%, protein >40 mg/dl and sugar <40 mg/dl or less than 2/3rd of parallel blood sugar was found. CSF antigen detection, PCR and MRI was not considered as the lack of infrastructure and also due economical infeasibility.[7]

Viral encephalitis

CSF with features of lymphocytic pleocytosis (5 to 500 cells/ml), mildly elevated protein content (30 to 65 mg/dl) and normal glucose content. Normal CSF examination does not eliminate the possibility of viral encephalitis.[8]

Complex febrile convulsion

A seizure occurring in association with a febrile illness (temp >38.3-degree Celsius), in the absence of central nervous system infection or acute electrolyte imbalance in children older than 1 month of age upto 5 years without prior afebrile seizures. It is considered complex if it is focal, prolonged (lasting for more than 15 minutes or multiple (occurrence of more than one seizure during the febrile illness).[9]

Dengue encephalopathy

Acute encephalopathy is the most commonly reported neurological disorder associated with dengue virus

infection. Dengue encephalopathy involves a diminished level of consciousness that can be precipitated or caused by several factors, including prolonged shock, anoxia, cerebral oedema, metabolic disturbances (e.g. hyponatraemia), systemic or cerebral haemorrhages, acute liver failure, or renal failure. CSF analyses, including measurements of protein, glucose, and cell count, are usually normal.[10]

Acute encephalopathy

Generalized disorder of cerebral function (cognitive disorders, convulsions, and mood/personality disorders) that is acute onset with normal CSF findings, with radiological evidence of encephalopathy, non-specific. It can be autoimmune, idiopathic, or metabolic.[11]

Statistical analysis

The collected data were analysed using statistical package for the social sciences (SPSS) software version 20. For Descriptive statistics standard deviation was used whereas inferential statistics chi square test was used. P value less than 0.05 was taken as significant level.

RESULTS

Total admissions in the ward from the period of January 2021 to December 2021, who were belonging to age 1 month to 12 years were 3086. Out of which, a total of 123 children were clinically suspected of bacterial meningitis were included in the study. Among them 104 patients were diagnosed as a case of bacterial meningitis. Rest were diagnosed as viral encephalitis-7, complex febrile convulsions-4, dengue encephalopathy-4, acute encephalopathy-3, and inborn error of metabolism-1. The majority of children (46.15%) were from the age group of 1 month to 1 year with mean age of patients was 28.30±1.23 months, ranging from 1month to 12 years. The male to female ratio was 1.08:1 (Table 1).

Table 1: Distribution of patients according to age and gender (n=104).

Age (years)	No. of patients			Percent-age
	Male	Female	Total	
1 month to 1 year	34	14	48	46.15
>1 to 3	10	7	17	16.35
>3 to 6	7	15	22	21.15
>6 to 12	3	14	17	16.35
Total	54	50	104	100
Mean ±SD	28.30±1.23 months (ranged: 1 month-12 years)			

Fever (93.26%) and altered sensorium (92.30%), were the commonest presenting features and neck rigidity (58.65%) was the commonest meningeal sign. Rest of the data are enumerated in the Table 2.

Table 2: Clinical features of patients.

Clinical features	No. of patients	Percentage
Symptoms		
Fever	97	93.26
Altered sensorium	96	92.30
Convulsions	93	89.42
Vomiting	37	35.57
Headache	26	25.00
Irritability	22	21.15
Signs		
Meningeal signs		
Neck rigidity	61	58.65
Kernig sign	41	39.42
Brudzinski sign	35	33.65
Tachycardia	63	60.58
Febrile on admission	34	32.69
Shock	19	18.26
Cushing's triad	14	13.46
Hepatomegaly	5	4.81
Splenomegaly	3	2.88

Table 3: Distribution of patients according to neurologic assessment (n=104).

Neurologic assessment	No. of patients	Percentage
Mental status (higher function)		
Abnormal	36	34.61
Normal	68	65.38
Glasgow coma scale		
<8/15	14	13.46
8/15- 12/15	22	21.75
>12/15	68	65.38
Cranial nerve examination		
Normal	93	89.42
Abnormal	11	10.57
VI^{th}	6	5.77
VII^{th}	3	2.88
IX^{th}/ X^{th}	2	1.92
Motor examination		
Normal	90	86.53
Hypo/ hypertonia	11	10.58
Focal motor deficit	3	2.88
Deep tendon reflexes		
Normal	59	56.73
Depressed	27	25.96
Exaggerated	18	17.30
Plantar		
Flexor	59	56.73
Extensor	32	30.77
Absent	13	12.50

Developmental milestones were delayed in 5 (4.80%) cases, out of which 4 had a history of NICU stay in their

earlier life. Immunization based on national immunization schedule was partially received by 13 (12.50%) and 10 (9.61%) children did not receive any vaccines at all. The neurologic assessment showed abnormal mental status (34.61%), abnormal cranial nerve examination findings (10.57%) and abnormal motor function (13.46%) (Table 3).

Among the total 123 patients, who were suspected of meningitis, final diagnosis of bacterial meningitis was done based of CSF examination report, among which 58 (55.77%) of the cases had a positive culture report. Among those who had negative reports (46 cases), diagnosis was established based on CSF protein, CSF sugar and CSF microscopy reports. Among the culture negative cases, routine microscopy was found to be normal in 3 cases, all of which had received some antibiotics before CSF examination. CSF Analysis are shown in Table 4. The mean protein levels in children were 74.22 mg% and the mean CSF sugar in the study group was 58.2 mg%.

Table 4: Summary of analysis.

Summary of analysis	Normal (%)	Abnormal (%)
Culture positive: 58		
Protein	22 (37.93)	36 (62.06)
Sugar	19 (32.75)	39 (67.24)
Routine microscopy	25 (43.10)	33 (56.89)
Culture negative: 46		
Protein	0 (0.0)	46 (100.0)
Sugar	0 (0.0)	46 (100.0)
Routine microscopy	3 (6.52)	43 (93.47)
CSF analysis	**No. of patients**	**Percentage**
Predominant CSF cells		
Polymorphs	70	67.30
Lymphocytes	06	5.76
No cells	28	26.92
CSF protein (mg%)		
<45	22	21.15
45–100	06	5.76
>100	76	73.07
CSF sugar (mg/dl)		
<40/<2/3rd RBSL	85	81.73
>40	19	18.26

Among the organisms grown in CSF culture pneumococcus was the most commonly isolated one accounting for 53.48% of the cases as depicted in Figure 2. The growth in the CSF revealed that ceftriaxone was sensitive in maximum i.e., 38 of the cases (65.51%), followed by cefotaxime 30 (51.72%) and amikacin (39.65%).

Among the total 123 patients, 104 (84.55%) diagnosed with bacterial meningitis and remaining 19 (15.44%) cases diagnosed other than meningitis. It was observed that CRP in CSF was positive in maximum number of children with bacterial meningitis i.e., 86 (82.69%) but it was negative in 18 (17.30%) children. In children diagnosed other than meningitis, CRP was positive in 3 (15.78%) cases and negative in 16 (84.21%). The mean CRP level was 15.36±0.67 mg/l in children with meningitis.

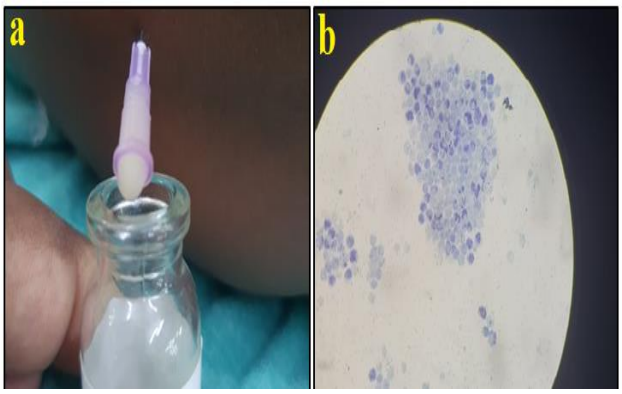

Figure 1: (a) CSF examination performed, which shows purulent cerebrospinal fluid, and (b) CSF routine microscopy of the above patient.

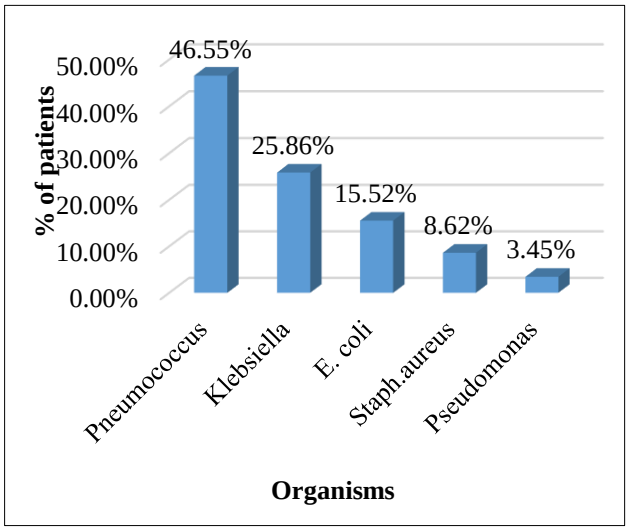

Figure 2: Organisms grown in CSF culture (n=58).

Among the culture positive patients, 53 (91.37%) out of 58, showed positive CSF CRP levels. Comparing cytology reports with CSF CRP positivity, 62 (81.57%) out of 76 abnormal cytology reports were found to be positive. In contrasting abnormal CSF biochemical reports with CSF CRP positivity, 66 (80.48%) out of 82 were found to be positive as show in Table 5.

Among 90 patients who were discharged, 84 (80.76%) had no new neurological deficit, but 6 of the discharged patients had neurological deficit. This included 3 patients which had facial nerve palsy, 3 with mild motor deficits. The institutional mortality of the study was 13.46%. (Figure 3).

Table 5: CSF C-reactive protein with individual CSF parameters.

CSF	CSF CRP positive (%)	CSF CRP negative (%)
CSF culture (total diagnosed patients: 108)		
Culture positive: 58	53 (91.37)	5 (8.62)
Culture negative: 46	33 (71.73)	13 (28.26)
CSF cytology (total diagnosed patients: 108)		
Abnormal: 76	62 (81.57)	14 (18.42)
Normal: 28	24 (85.71)	4 (14.28)
CSF biochemical study (total diagnosed patients: 108)		
Abnormal: 82	66 (80.48)	16 (19.51)
Normal: 22	20 (90.91)	2 (9.09)

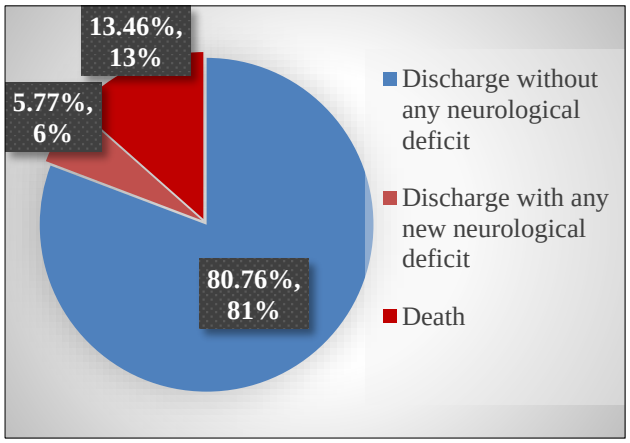

Figure 3: Distribution of patients according to outcome (n=104).

Among 104 bacterial meningitis cases, 86 children (82.69%) had CSF CRP positivity (sensitivity 83%) and CSF culture was negative for 16 children among 19 children who tested to be CSF CRP negative (specificity 84.21%). Out of the total 89 children who show CSF CRP positivity, 86 meningitis patients had some organism grown in their CSF culture (positive predictive value 96.62%) and CSF culture was negative for 16 non meningitis children among total 34 children who tested to be CSF CRP negative (negative predictive value 47.05%).

DISCUSSION

The institutional prevalence of bacterial meningitis in our tertiary care hospital was 3.37% which was low compared to with study conducted by Banu et al (2021) (7.5%).[12] On contrary, a higher prevalence of bacterial meningitis was reported in Indian studies conducted in Kolkata by Joardar et al (2012) (34.66%) and in Tamil Nadu by Minz et al (2008) (18.56%).[13,14] The lower incidence may be attributed to an improved vaccination coverage, and better social environment achieved over years. Among the 104 cases of bacterial meningitis, majority i.e., 46.15% were belonging to the age group of 1 month to 1 year, making it the most vulnerable population to be affected by bacterial meningitis. The mean age of patients was 28.30±1.23 months, ranging from 1 month to 12 years with near equitable gender division (male: 51.92%). These findings are comparable with the previous studies.[15,16]

Fever was a most common presenting complaints for the cases with bacterial meningitis followed by altered sensorium. The most common meningeal sign was neck rigidity. A similar observation was also recorded by other authors.[17,18] Developmental milestones were delayed in 5 (4.80%) cases, out of which 4 had a history of NICU stay in their earlier life. Immunization based on national immunization schedule was partially received by 13 (12.50%) and 10 (9.61%) children did not receive any vaccines at all. The neurologic assessment show that the mental status was abnormal in 34.61% of children. 14 out of the 104 patients required assisted breathing on admission in view of GCS score less than 8/15. Cranial nerve involvement was seen in 11 patients, of which maximum had lateral rectus palsy (VIth nerve). Tone and power abnormality were observed in 14 patients (13.46 %).

Among 104 bacterial meningitis cases, 58 (55.76%) had a positive culture report. Among the culture negative cases, routine microscopy was found to be normal in 3 cases, all of which had received some antibiotics before CSF examination. Although 73.07% of the cases had cells in the CSF, mostly polymorphs (67.30%) and 6 (5.76%) cases had predominantly lymphocytes, the rest of the 28 cases did not show any significant cells. The reason for this observation may be due to inadvertent delay in CSF processing which may cause desiccation of cells, previous antibiotic administration, variable skill factor of the pathologist examining the CSF.[17] In present study, CSF in the bacterial meningitis group was most commonly clear. It was turbid or frankly purulent in only 11.2% of cases. The mean protein levels in children were 138.4 mg% and mean CSF sugar level was 32.2 mg%. These findings are in accordance with the study conducted by Bansal et al and Kalpana et al.[15,17]

Among the organisms grown in CSF culture pneumococcus (*Streptococcus pneumoniae*) was the most commonly isolated one accounting for 46.55% of the 58 CSF culture positive cases. This can be attributed to the lack of immunization coverage of pneumococcal vaccine among socioeconomically weak families that are being catered by the centre. The similar observations were made by other studies done elsewhere, where the most common isolates were streptococcus pneumonia.[19,20]

Among the total 123 patients, 104 (84.55%) diagnosed with bacterial meningitis and remaining 19 (15.44%) cases had a diagnosis other than meningitis. It was observed that CRP in CSF was positive in maximum number of children with bacterial meningitis i.e., 86 (82.69%) but it was negative in 18 (17.30%) children. In children diagnosed

other than meningitis, CRP was positive in 3 (15.78%) cases and negative in 16 (84.21%). These findings are in hands with previous studies by Bansal et al, and Hansson et al.[15,21]

Out of 104 children 58 were CSF culture positive of them 53 (91.37%) were CSF-CRP positive and 5 (8.62%) cases were CSF-CRP negative. Whereas 46 children were CSF culture negative, out of them 33 (71.73%) were CSF-CRP positive and 13 (28.26%) were CSF-CRP negative. CSF cytology was abnormal in 76 children and normal in 28 children. Among 76 children, 62 (81.57%) were CSF-CRP positive and remaining 14 (18.42%) were CSF-CRP negative. While among 28 children, 24 (85.71%) were CSF-CRP positive and 4 (14.28%) were CSF-CRP negative. However, CSF biochemical study was abnormal in 85 cases and normal in 19 cases. Among the abnormal cases, 76 (89.41%) were CSF-CRP positive and 9 (10.58%) were CSF-CRP negative. Whereas out of normal cases, 10 (52.63%) were CSF-CRP positive and 9 (47.36%) were CSF-CRP negative. The current study suggests that a higher number of false negatives value of CSF-CRP were observed in lesser age group that too less than 3 years of age. Our results correlated with other studies.[17,22] The institute mortality of patients with bacterial meningitis was 13.46% which is comparable with the previous studies.[23,24]

CRP in CSF was positive in 86 (82.69%) of the CSF samples with culture positivity which was statistically significant ($p<0.01$) in detecting cases of bacterial meningitis. The sensitivity was 83% and specificity was 84.21%. It had a positive predictive value of 96.62% and a negative predictive value of 47.05%. So, though CSF CRP is reasonably sensitive in picking up cases of pyrogenic meningitis; it can miss up to 17% of the cases. But it is highly specific for bacterial meningitis. So, if CSF CRP is positive, it virtually makes a diagnosis of bacterial meningitis irrespective of other corroborative evidence whereas a negative test need not necessarily rule out pyogenic meningitis. A similar finding was also reported in various other studies.[5,19,22]

The level of CRP in CSF is variable and usually less than that of plasma. It depends on the amount of CRP released into CSF from plasma by ultrafiltration and secretion by inflamed meninges. Among all these mechanisms, CSF leakage or passive diffusion from the blood appears more plausible rather than active secretion.[25] In current study, the CSF-CRP was higher in the bacterial meningitis group, indicating some amount of active secretion in CSF. CSF-CRP also had a good correlation with other CSF parameters. Currently, the gold standard for the diagnosis of meningitis is CSF culture. But it has its own drawbacks such as the low positivity rate and chances of contamination. The CSF picture can also be altered by administrating antibiotics, delayed analysis, and in partially treated meningitis. CSF-CRP can come as a handy investigation in such settings whose level is not affected when it is analysed early in the course of illness.

Limitations

This study was limited by a small sample size and lack of quantitative estimation of CSF-CRP. A larger sample size and quantitative estimation of CSF-CRP would have given a better insight. No serial CSF-CRP levels were tested to see the response to the treatment, but this would have required repeated LPs, which is not ethically justifiable. We have also not compared our results with other markers such as CSF procalcitonin and IL-6.

CONCLUSION

In the present study, CRP levels in CSF offers a moderate sensitivity and specificity as well as high positive predictive value. This indicates that CSF CRP is a better marker in differentiating bacterial meningitis. Also, it can be concluded that, in addition to current conventional diagnostic methods (biochemistry, cultures and smears), CSF-CRP is a simple, rapid, and accurate approach for the laboratory diagnosis of bacterial meningitis. It can be used as an initial test for the diagnosis of bacterial meningitis till other confirmatory test reports are awaited. Thus, while concluding that CSF CRP levels can serve as a useful screening test for bacterial meningitis, a further study with a larger population is required to validate our results. Measuring CRP levels before and after antibiotics would also give a better interpretation.

Recommendations

CSF CRP can be used as a bedside diagnostic tool for the rapid diagnosis of bacterial meningitis in children. It should be made available in every paediatric ICU. It is economical, quick and have high positive predictive value with good sensitivity. Current guidelines for empirical antibiotics for the treatment of bacterial meningitis can be used with good coverage for the common pathogens found in the community.

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