Original Investigation / *Özgün Araştırma*

DOI: 10.5578/ced.20239802 • *J Pediatr Inf 2023;17(2):e79-e90*

Evaluation of Clinical and Laboratory Findings of Children with Acute Bacterial and Enteroviral Meningitis

Akut Bakteriyel ve Enteroviral Menenjiti Olan Çocukların Klinik ve Laboratuvar Bulgularının Değerlendirilmesi

Aygün Babayeva[1](İD), Melike Emiroğlu[2](İD), Gülsüm Alkan[2](İD), Uğur Arslan[3](İD)

[1] Department of Pediatric Health and Diseases, Selçuk University Faculty of Medicine, Konya, Türkiye
[2] Division of Pediatric Infectious Diseases, Department of Pediatrics, Selçuk University Faculty of Medicine, Konya, Türkiye
[3] Department of Medical Microbiology, Selçuk University Faculty of Medicine, Konya, Türkiye

Cite this article as: Babayeva A, Emiroğlu M, Alkan G, Arslan U. Evaluation of clinical and laboratory findings of children with acute bacterial and enteroviral meningitis. J Pediatr Inf 2023;17(2):e79-e90.

Abstract

Objective: Acute meningitis is one of the important infectious diseases that can result in mortality and morbidity in children despite effective treatment and vaccination. Early diagnosis of the disease, isolation of the causative agent, and appropriate treatment are important in preventing the development of complications. In this study, we aimed to examine the clinical, laboratory findings and agent distributions of patients with acute meningitis for the last seven years. In addition, findings that may be significant in the differentiation of bacterial-enteroviral meningitis were investigated.

Material and Methods: Patients who underwent cerebrospinal fluid (CSF) examination with the pre-diagnosis of acute meningitis at Selçuk University Faculty of Medicine, Pediatric Infectious Diseases Service between September 2013 and September 2020 were evaluated retrospectively. The patients who were diagnosed as other than meningitis, chronic meningitis, and ventriculoperitoneal shunt meningitis were excluded from the study.

Results: The data of 48 pediatric patients diagnosed with acute bacterial meningitis (n= 22) and enteroviral meningitis (n= 26) out of 177 patients who underwent CSF examination with the diagnosis of acute meningitis were retrospectively analyzed. The mean age of the patients was 83.46 ± 62.68 months, and 79.2% of them were male. *S. pneumoniae*, *N. meningitidis*, *E. coli*, *H. influenzae* type b were detected in patients with bacterial meningitis. All patients with enterovirus meningitis were diagnosed by CSF polymerase chain reaction (PCR). In patients with bacterial meningitis, posivity of CSF PCR, CSF culture and blood culture was 86.3%, 50%,

Öz

Giriş: Akut menenjit, çocuklarda etkin tedavi ve aşılamaya rağmen mortalite ve morbiditeyle sonuçlanabilen önemli enfeksiyon hastalıklarındandır. Hastalığın erken tanısı, etkenin izolasyonu ve uygun tedavi komplikasyon gelişimini önlemede önemlidir. Bu çalışmada yedi yılda akut menenjit tanısı alan çocuk hastaların klinik, laboratuvar bulguları ve etken dağılımlarının incelenmesi amaçlanmıştır. Ayrıca, bakteriyel-enteroviral menenjit ayrımında anlamlı olabilecek bulgular araştırılmıştır.

Gereç ve Yöntemler: Eylül 2013-Eylül 2020 tarihleri arasında Selçuk Tıp Fakültesi, Çocuk Enfeksiyon Hastalıkları Servisinde akut menenjit ön tanısıyla beyin omurilik sıvısı (BOS) incelemesi yapılan hastalar retrospektif olarak değerlendirildi. Hastalardan menenjit dışı tanı alanlar, kronik menenjit etkenleri saptananlar ve ventriküloperitoneal şant menenjiti olanlar çalışma dışı bırakıldı.

Bulgular: Akut menenjit tanısıyla BOS incelemesi yapılan 177 hastadan, akut bakteriyel menenjit (n= 22) ve enteroviral menenjit (n= 26) tanısı alan 48 çocuk hasta ileri incelemeye alındı. Hastaların yaş ortalaması 83.46 ± 62.68 ay olup %79.2'si erkekti. Bakteriyel menenjiti olan hastalarda etken olarak *S. pneumoniae*, *N. meningitidis*, *E. coli*, *H. influenzae* tip b saptandı. Enterovirüs menenjiti olan hastaların tamamında tanı, BOS polimeraz zincir reaksiyon (PCR) testi incelemesiyle konuldu. Bakteriyel menenjiti olan hastalarda BOS PCR testi pozitifliği %86.3, BOS kültüründe üreme %50, ve kan kültüründe üreme %27.3 olarak saptandı. Bakteriyel menenjiti olup BOS PCR testi negatif sonuçlanan üç hastanın kan kültüründe üreme oldu. Bakteriyel menenjiti olan hastalarda BOS glukoz ve protein düzeyleri, kanda lökosit sayısı, C-reaktif protein (CRP) ve pro-

Correspondence Address/Yazışma Adresi
Gülsüm Alkan
Selçuk Üniversitesi Tıp Fakültesi,
Çocuk Enfeksiyon Hastalıkları Bilim Dalı,
Konya-Türkiye
E-mail: galkan-85@hotmail.com

Received: 23.09.2022 **Accepted:** 26.02.2023 **Available Online Date:** 23.06.2023

and 27.3%, respectively. Although the CSF PCR of three patients with bacterial meningitis was negative, bacterial growth was detected in the blood culture. CSF glucose and protein levels, blood leukocyte count, C-reactive protein (CRP) and procalcitonin levels were significantly higher in patients with bacterial meningitis compared to patients with enteroviral meningitis. A procalcitonin value of 0.855 ng/mL and above was found in favor of bacterial meningitis (p= 0.001).

Conclusion: CSF PCR test plays an important role in the diagnosis of acute meningitis and in distinguishing between viral and bacterial meningitis. Detection of enterovirus can provide allowing earlier discharges and decreasing avoidable inappropriate antibiotic treatments.

Keywords: Meningitis, bacterial meningitis, viral meningitis, enterovirus, children

kalsitonin düzeyleri, enteroviral menenjiti olan hastalara göre anlamlı düzeyde yüksekti. Prokalsitonin değerinin 0.855 ng/mL ve üzerinde olması bakteriyel menenjit lehine bulundu (p= 0.001).

Sonuç: Akut menenjiti tanısında ve viral ve bakteriyel menenjit ayrımı yapmada BOS PCR testi önemli rol oynamaktadır. BOS PCR testinde enterovirüsün saptanması hastaların erken taburculuklarını sağlamakta ve uygunsuz antibiyotik tedavilerini azaltmaktadır.

Anahtar Kelimeler: Menenjit, bakteriyel menenjit, viral menenjit, enterovirüs, çocuklar

Introduction

Meningitis is the inflammation of the meningeal membranes surrounding the brain and spinal cord, and the pia, arachnoid and subarachnoid distance is affected. Viruses are the most common cause of acute meningitis and are responsible for approximately 90% of acute meningitis cases. Enteroviruses are the most common cause of viral meningitis. However, fungi and parasites, especially bacteria, can also cause meningitis. The most common bacterial meningitis agents in childhood are *Streptococcus pneumoniae* (*S. pneumoniae*), *Neisseria meningitidis* (*N. meningitidis*) and *Haemophilus* influenzae type b (*H. influenzae* type b) (1).

With the development of conjugated bacterial vaccines and their inclusion in national vaccine schemes, the incidence of bacterial meningitis has been significantly reduced especially in children. However, bacterial meningitis in childhood is a serious infectious disease with high mortality and morbidity.

Therefore, early diagnosis and treatment is important. The aim of this retrospective study was to examine the clinical, laboratory findings and distribution of agents in pediatric patients diagnosed with acute meningitis. In addition, the evaluation of clinical and laboratory findings of children with bacterial and enteroviral meningitis, and investigation of clinical and laboratory findings that may help in the differentiation of bacterial and enteroviral meningitis.

Materials and Methods

This retrospective study was conducted at Selçuk University Faculty of Medicine between September 2013 and September 2020.

One hundred seventy-seven patients between the ages of 0-20 years hospitalized with a prediagnosis of acute meningitis in the pediatric infectious diseases service of our hospital were included into the study.

Patient data was received from the hospital automation system and archive retrospectively.

(The date and number of Selçuk University Local Ethics Committee approval: 2020/82). Meningitis classification of the patients was made according to the definitions of the World Health Organization stated below (2).

Definite bacterial meningitis: If any of the following;

- Positive cerebrospinal fluid (CSF) polymerase chain reaction (PCR) test or,
- CSF or blood culture growth or
- Positive CSF Gram staining.

Aseptic meningitis: Pleocytosis in CSF (at least five leukocytes/mm^3) in patient with symptoms of acute onset meningitis and the absence of any applicable laboratory criteria for the diagnosis of bacterial meningitis.

Aseptic meningitis is divided into two subgroups:

1) Viral meningitis: Detection of viral agent in CSF PCR test,
2) Unspecified meningitis.

Out of 177 patients hospitalized with the diagnosis of acute meningitis and treated and examined, 74 received a diagnosis other than meningitis and were excluded from the study.

In addition, cases with meningitis due to factors with different clinical course such as tuberculosis and brucella were also excluded.

Patients with possible bacterial meningitis were excluded from the study. Meningitis due to other viral agents, which are very few and may adversely affect the reliability of the study and a special group of patients, immunodeficient patients with ventriculoperitoneal shunt meningitis, were excluded from the study. As a result, 48 pediatric patients with acute bacterial or enteroviral meningitis were included in the study. Demographic data, clinical, laboratory and imaging findings of the patients, and the treatment they received were recorded and subjected to further statistical analysis.

Statistical Analysis

Data were analyzed with IBM SPSS V23. Conformity to the normal distribution was evaluated using the Shapiro-Wilk test.

In the comparison of normally distributed data according to dual groups, the independent two sample t-test was used to compare normally distributed data and

Mann-Whitney U test was used for the comparison of non-normally distributed data. The relation between categorical variables according to groups was analyzed using Yates correction, Pearson Chi-square and Fisher's exact test.

For bacterial meningitis, ROC analysis was used to determine the cut-off values of leukocyte, neutrophil, C-reactive protein (CRP) and procalcitonin (PCT) values.

Analysis results were expressed as mean ± standard deviation for quantitative data and median (minimum-maximum) and frequency (percentage) for categorical variables. Significance level was set as p< 0.05.

Results

Our study included 48 pediatric patients, 38 boys and 10 girls. Median age of the patients was 72 (min-max= 2-240) months (Table 1).

Enteroviral meningitis was found in 26 patients and bacterial meningitis was found in 22 patients. In terms of age and sex, no statistically significant difference was observed between patients with enteroviral and bacterial meningitis (Table 1).

When the complaints of the patients were evaluated, it was found that the most common complaints in both groups were fever, headache and vomiting were observed, but there was no statistically significant difference between the two groups (Table 1).

When physical examination (PE) findings of the patients at the time of admission were evaluated, the most common finding was nuchal rigidity. However, in terms of admission PE findings, no statistically significant difference was observed between patients with bacterial and enteroviral meningitis (Table 2).

No statistically significant difference was observed between patients with enteroviral and bacterial meningitis in terms of antibiotic treatment prior to admission to our hospital and previous history that may be a risk factor for meningitis trauma, smoking at home, and underlying disease (p= 0.713, p= 0.081, p= 0.183, p= 0.223, respectively). In both groups only one patient was incompletely vaccinated and statistical evaluation could not be made.

No statistically significant difference was observed between patients with enteroviral and bacterial meningitis in terms of CSF pressure and appearance during LP (Table 3).

H. influenzae type b was found in one of 22 patients with bacterial meningitis, *E. coli* in two, *N. meningitidis* in four, and *S. pneumoniae* in 15 patients. In patients with bacterial meningitis, CSF PCR positivity was 86.3%, growth in CSF culture was 50%, and CSF Gram staining was 27.3%. There were three patients with bacterial meningitis and negative CSF PCR test results. Two of them were *E. coli* meningitis and were diagnosed only by growth in CSF culture. One of the patients was two months old and the other was six months old. The third patient had *S. pneumoniae* meningitis diagnosed only by growth in blood culture. The patient with *H. influenzae* type b meningitis diagnosed by CSF PCR was 15 years old and had post-traumatic meningitis. Only gram-positive cocci were observed on Gram staining, all of which were detected in *S. pneumoniae* meningitis. *S. pneumonia* was also detected in the PCR test and CSF culture of all those with positive Gram staining, while growth was observed in the blood culture of three of them. Reproduction was detected in the blood culture of 27.3% of the patients with bacterial meningitis, all of which belonged to *S. pneumoniae*. It was observed that the most effective examination in diagnosing bacterial meningitis was CSF PCR examination (Table 3).

All patients with acute meningitis received antibiotic therapy. However, in patients with bacterial meningitis, vancomycin combination was needed more (p= 0.009) (Table 3).

Due to the fact that there were periodical changes in the duration of receiving results for CSF PCR and the irregularity of the patient's application distribution, the effect of the PCR test could on the duration of antibiotics use could not be evaluated.

Antibiotic treatment of patients with enterovirus positivity in CSF PCR treatment was discontinued.

Imaging of 25 patients in total (only CT in seven patients, MRI only in seven patients, CT + MR in 11 patients) was made. Eleven patients were requested first CT and then MR imaging. MR imaging was performed at a higher rate in patients with bacterial meningitis (p= 0.011), meningeal involvement (p= 0.038), subdural infection (p= 0.038), and intracranial bleeding (p= 0.038) were observed more frequently in patients with bacterial meningitis.

While CSF glucose value was found to be lower in patients with bacterial meningitis (p< 0.001), no difference was observed between the groups in concurrent blood glucose values. CSF protein was higher in the bacterial meningitis group (p= 0.013). No significant difference was observed in CSF chloride, leukocyte, neutrophil and lymphocyte counts (Table 4).

When acute phase reactants were evaluated according to whether they were high or not, they were found higher in the bacterial meningitis group (p= 0.010). Neutrophil count in complete blood count was found to be higher in patients with

Table 1. Comparison of categorical variables by groups

	Bacterial meningitis	Enteroviral meningitis	Total	Test stat.	p
	(n= 22)	(n= 26)			
Sex					
Male	17 (77.3)	21 (80.8)	38 (79.2)	---	1.000***
Female	5 (22.7)	5 (19.2)	10 (20.8)		
Presenting symptoms					
Fever					
Yes	19 (86.4)	18 (69.2)	37 (77.1)	1.129	0.288**
No	3 (13.6)	8 (30.8)	11 (22.9)		
Headache					
Yes	9 (40.9)	19 (73.1)	28 (58.3)	3.836	0.050**
No	13 (59.1)	7 (26.9)	20 (41.7)		
Vomiting					
Yes	13 (59.1)	18 (69.2)	31 (64.6)	0.184	0.668**
No	9 (40.9)	8 (30.8)	17 (35.4)		
Seizure					
Yes	3 (13.6)	1 (3.8)	4 (8.3)	---	0.320***
No	19 (86.4)	25 (96.2)	44 (91.7)		
Altered consciousness					
Yes	1 (4.5)	0 (0)	1 (2.1)	---	---
No	21 (95.5)	26 (100)	47 (97.9)		
Focal neurological finding					
Yes	2 (9.1)	0 (0)	2 (4.2)	---	---
No	20 (90.9)	26 (100)	46 (95.8)		
Photofobia					
No	22 (100)	26 (100)	48 (100)	---	---
Rash					
No	22 (100)	26 (100)	48 (100)	---	---
Predisposition to sleep					
No	22 (100)	26 (100)	48 (100)	---	---
Unease					
Yes	2 (9.1)	2 (7.7)	4 (8.3)	---	1.000***
No	20 (90.9)	24 (92.3)	44 (91.7)		

*Pearson Chi-square test, **Yates correction, ***Fisher's exact test.

bacterial meningitis than in patients with enteroviral meningitis (p= 0.011) (Table 4).

CRP and PCT values in patients with bacterial meningitis were found to be higher than those with enteroviral meningitis (p= 0.005 and p< 0.001, respectively). No difference was observed between groups in ESR value (Table 4).

AUC value of the PCT parameter for bacterial meningitis was statistically significant as 0.855. (p= 0.001).

When the cut-off value of PCT was taken as 0.20, sensitivity was 82.4%, specificity was 80%, PPV was 82.4% and NPV was obtained as 80%. Since the AUC values of the other parameters were not obtained to be significant, a cut-off value was not determined (p> 0.050) (Figure 1).

Table 2. Comparison of physical examination findings of patients with bacterial and enteroviral meningitis

	Bacterial meningitis	Enteroviral meningitis	Total	Test stat.	p
	(n= 22)	(n= 26)			
Physical examination					
Neck rigidity					
Yes	12 (54.5)	10 (38.5)	22 (45.8)	0.678	0.410**
No	10 (45.5)	16 (61.5)	26 (54.2)		
Brudzinski finding					
Yes	5 (22.7)	5 (19.2)	10 (20.8)	---	1.000***
No	17 (77.3)	21 (80.8)	38 (79.2)		
Kerning finding					
Yes	6 (27.3)	3 (11.5)	9 (18.8)	---	0.267***
No	16 (72.7)	23 (88.5)	39 (81.3)		
Seizure					
Yes	3 (13.6)	0 (0)	3 (6.3)	---	0.089***
No	19 (86.4)	26 (100)	45 (93.8)		
Predisposition to sleep					
Yes	1 (4.5)	0 (0)	1 (2.1)	---	---
No	21 (95.5)	26 (100)	47 (97.9)		
Focal neurological finding					
Yes	1 (4.5)	0 (0)	1 (2.1)	---	---
No	21 (95.5)	26 (100)	47 (97.9)		
Photofobia					
Yes	1 (4.5)	0 (0)	1 (2.1)	---	---
No	21 (95.5)	26 (100)	47 (97.9)		
Rash					
Yes	0 (0)	1 (3.8)	1 (2.1)	---	---
No	22 (100)	25 (96.2)	47 (97.9)		
Distress					
Yes	1 (4.5)	2 (7.7)	3 (6.3)	---	1.000***
No	21 (95.5)	24 (92.3)	45 (93.8)		
Fundus					
Yes	3 (13.6)	1 (3.8)	4 (8.3)	---	0.320***
No	19 (86.4)	25 (96.2)	44 (91.7)		
Shock hypotension on presentetion					
No	22 (100)	26 (100)	48 (100)	---	---
Glaskow coma score					
8-11	2 (9.1)	0 (0)	2 (4.2)	---	---
12-15	20 (90.9)	26 (100)	46 (95.8)		

*Pearson Chi-square test, **Yates correction, ***Fisher's exact test.

Table 3. Comparison of CSF findings of patients with bacterial and enteroviral meningitis

	Bacterial meningitis	Enteroviral meningitis	Total	Test stat.	p
	(n= 22)	(n= 26)			
Specific diagnosis					
Escherichia coli meningitis	2 (9.1)	0 (0)	2 (4.2)	---	---
Enteroviral meningitis	0 (0)	26 (100)	26 (54.2)		
Haemophilus influenzae meningitis	1 (4.5)	0 (0)	1 (2.1)		
Neisseria meningitidis meningitis	4 (18.2)	0 (0)	4 (8.3)		
Streptococcus pneumoniae meningitis	15 (68.2)	0 (0)	15 (31.3)		
CSF pressure					
High	5 (22.7)	1 (3.8)	6 (12.5)	---	0.081***
Not measured	17 (77.3)	25 (96.2)	42 (87.5)		
CSF appearnace					
Clear	20 (90.9)	26 (100)	46 (95.8)	---	---
Blurred	2 (9.1)	0 (0)	2 (4.2)		
Growth in CSF culture					
Escherichia coli	2 (9.1)	0 (0)	2 (4.2)	---	---
Neisseria meningitidis	1 (4.5)	0 (0)	1 (2.1)		
Streptococcus pneumoniae	8 (36.4)	0 (0)	8 (16.7)		
No growth	11 (50)	26 (100)	37 (77.1)		
BOS PCR					
Enterovirus	0 (0)	26 (100)	26 (54.2)	---	---
Haemophilus influenzae	1 (4.5)	0 (0)	1 (2.1)		
Neisseria meningitidis	4 (18.2)	0 (0)	4 (8.3)		
Streptococcus pneumoniae	14 (63.6)	0 (0)	14 (29.2)		
Negative	3 (13.6)	0 (0)	3 (6.3)		
Gram staining					
Gram-positive coccus	6 (27.3)	0 (0)	6 (12.5)	---	**0.006*** **
Negative	16 (72.7)	26 (100)	42 (87.5)		
Growth in blood culture					
Streptococcus pneumoniae	6 (27.3)	0 (0)	6 (12.5)	---	**0.006*** **
No Growth	16 (72.7)	26 (100)	42 (87.5)		
Treatment					
Third generaion cephalosporin	12 (54.5)[a]	24 (92.3)[b]	36 (75)	9.331	**0.009***
Third generation cephalosporin + vancomycin	8 (36.4)[a]	2 (7.7)[b]	10 (20.8)		
Vancomycin + meropenem	2 (9.1)	0 (0)	2 (4.2)		

*Pearson Chi-square test, **Yates correction, ***Fisher's exact test,
[a-b]: There is no difference between groups with the same letter in each line.

Table 4. Comparison of quantitative laboratory values of patients with bacterial and enteroviral meningitis

	Bacterial meningitis		Enteroviral meningitis		Total		Test stat.	p
	Mean ± Standard deviation	Median (min-max)	Mean ± Standard deviation	Median (min-max)	Mean ± Standard deviation	Median (min-max)		
Age	92.82 ± 74.51	72.00 (2.00-240.00)	75.54 ± 50.79	72.00 (2.00-204.00)	83.46 ± 62.68	72.00 (2.00 - 240.00)	0.922	0.363*
Concurrent blood glucose	94.00 ± 26.10	90.00 (60.00-140.00)	93.62 ± 20.20	100.00 (48.00-135.00)	93.79 ± 22.84	99.00 (48.00 - 140.00)	0.058	0.954*
CSF chlorine	120.59 ± 5.16	121.00 (106.00-132.00)	123.27 ± 4.39	122.50 (118.00-142.00)	122.04 ± 4.89	122.00 (106.00 - 142.00)	207.5	0.102**
CSF protein	226.57 ± 209.90	191.50 (18.00-791.00)	96.85 ± 193.80	49.00 (24.00-1034.00)	156.30 ± 209.60	65.00 (18.00 - 1034.00)	166	**0.013****
CSF glucose	41.80 ± 23.50	49.00 (1.10-82.00)	62.73 ± 11.19	60.00 (42.00-92.00)	53.14 ± 20.60	56.50 (1.10 - 92.00)	-3.825	**0.001***
CSF leucocyte	703.18 ± 739.24	350.00 (0.00-2000.00)	516.15 ± 530.80	360.00 (0.00-2000.00)	601.88 ± 634.75	350.00 (0.00 - 2000.00)	235.5	0.289**
CSF neutrophil	559.36 ± 642.89	181.50 (0.00-2000.00)	358.54 ± 425.45	115.50 (0.00-1000.00)	450.58 ± 539.61	154.00 (0.00 - 2000.00)	231	0.249**
CSF lymphocyte	145.45 ± 354.91	0.00 (0.00-1386.00)	78.62 ± 222.51	0.00 (0.00-1000.00)	109.25 ± 289.40	0.00 (0.00 - 1386.00)	265	0.604**
Hemoglobin	11.91 ± 1.97	12.00 (8.00-16.00)	12.31 ± 1.12	12.00 (10.00-15.00)	12.13 ± 1.57	12.00 (8.00 - 16.00)	-0.839	0.408*
Hematocrit	35.68 ± 5.79	37.00 (23.00-46.00)	36.69 ± 3.40	36.00 (29.00-44.00)	36.23 ± 4.63	36.50 (23.00 - 46.00)	-0.72	0.477*
Leucocyte count	15486.36 ± 8291.67	13500.00 (3500.00-32000.00)	12750.00 ± 4641.66	12000.00 (6000.00-21000.00)	14004.17 ± 6639.08	12000.00 (3500.00 - 32000.00)	1.376	0.178*
Platelet count	346000.00 ± 290416.29	264000.00 (118000.00-1542000.00)	358461.54 ± 92209.43	336500.00 (224000.00-604000.00)	352750.00 ± 205539.72	329500.00 (118000.00 - 1542000.00)	198	0.069**
Neutrophil count	13754.55 ± 8048.35	12950.00 (2100.00-30000.00)	8557.69 ± 4355.06	8500.00 (1000.00-19000.00)	10939.58 ± 6773.38	9850.00 (1000.00 - 30000.00)	2.711	**0.011***
Lymphocyte count	2713.64 ± 2823.08	1500.00 (400.00-11000.00)	3111.54 ± 2498.85	2000.00 (100.00-10000.00)	2929.17 ± 2631.07	2000.00 (100.00 - 11000.00)	238	0.317**
Lymphocyte percentage	17.95 ± 14.34	13.10 (1.30-44.30)	21.85 ± 16.12	17.13 (6.60-66.00)	20.06 ± 15.30	15.60 (1.30 - 66.00)	224	0.199**
Neutrophil percentage	70.56 ± 21.96	70.50 (12.00-97.00)	69.99 ± 19.04	75.40 (17.00-88.90)	70.25 ± 20.20	73.54 (12.00 - 97.00)	266.5	0.687**
C-reactive protein	49.36 ± 70.63	12.50 (0.10-275.00)	11.27 ± 22.88	3.60 (0.02-101.00)	28.73 ± 53.62	7.00 (0.02 - 275.00)	150.5	**0.005****
Erythrocyte sedimentation rate	29.00 ± 26.45	26.50 (2.00-120.00)	23.75 ± 23.83	16.00 (2.00-120.00)	26.26 ± 24.97	18.50 (2.00 - 120.00)	232	0.481**
Procalcitonin	13.12 ± 17.97	1.70 (0.04-57.00)	0.41 ± 0.83	0.08 (0.00-2.90)	7.17 ± 14.44	0.21 (0.00 - 57.00)	37	**<0.001****

***Independent two sample t-test, **Mann-Whitney U test.

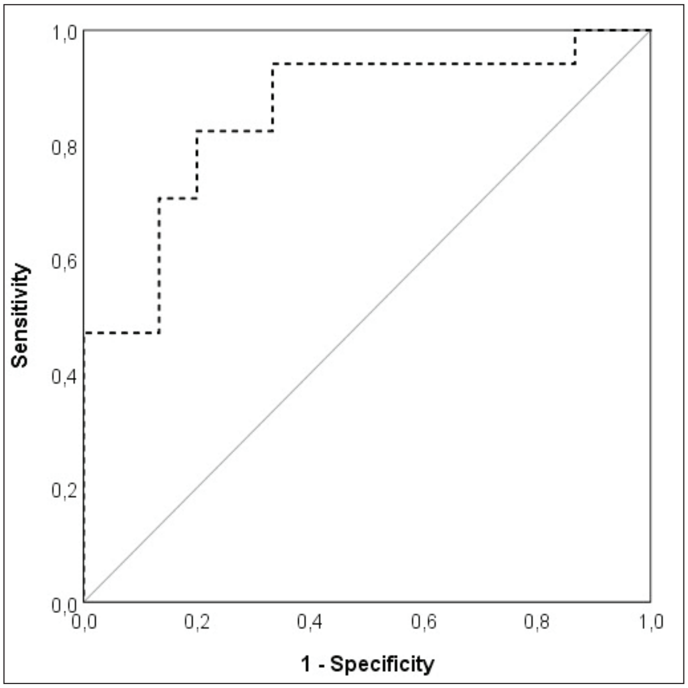

Figure 1. ROC curve of procalcitonin value.

Discussion

According to the World Health Organization, the incidence of bacterial meningitis in developed countries is 3/100.000 per year, while viral meningitis is 11/100.000 (3,4). Viruses are the most common cause of acute meningitis and are responsible for approximately 90% of acute meningitis cases. Enteroviruses are the most common cause of viral meningitis (>90%) (5). Bacteria that cause meningitis most in healthy children are *S. pneumoniae*, *H. influenzae* type b and *N. meningitidis* (6). With the introduction of conjugated vaccines into routine pediatric vaccination practices, a significant decrease was observed in *H. influenzae* type b and then *S. pneumoniae* meningitis (7-9). In a multicenter prospective surveillance study conducted in our country, it was observed that the incidence of acute bacterial meningitis, which was 3.5/100.000 in the 2005-2006 period, decreased to 0.9/100.000 in the 2011-2012 period, and this decrease was attributed to the inclusion of the *H. influenzae* type b vaccine in the national vaccination program in 2006 (10).

Studies in European countries conducted in different periods and in different countries between 1995 and 2012 found 50% *N. meningitidis,* 37% *S. pneumoniae*, 5% *H. influenzae* type b and other factors were found at a rate of 8% (11). Mayah et al., in their study in Egypt, have found *N. meningitidis* in 46.15%, *H. influenzae* type b in 30.77%, and *S. pneumoniae* in 23% of 26 children with bacterial meningitis (12).

In studies of different periods and centers in our country, *N. meningitidis* 5.5-71%, *S. pneumoniae* 10.3-61.1%, *H. influenzae* type b have been reported at a rate of 5.5-36.3 percent. Especially Mehmet Ceyhan's studies of consecutive periods, reflecting almost all regions of our country, put forward the change in meningitis factors.

When the cerebrospinal fluid samples of 1452 hospitalized children with meningitis were examined by culture and polymerase chain reaction test between 2005-2006, *N. meningitidis* was found as 51.6%, *S. pneumoniae* as 30.2%, *H. influenzae* type b as 18.1%. In the continuation of the same study, in a study of 96 children with bacterial meningitis between 2013 and 2014, it was reported that 90.4% of the patients were due to *N. meningitidis* and 9.6% of them were *S. pneumoniae* (10).

Again, in the study of Ceyhan et al., in which 125 children with bacterial meningitis were evaluated by PCR between 2015 and 2018, it was shown that 71% of them were *N. meningitidis,* 26.4% of them were *S. pneumoniae* and 2.4% of them were due to *H. influenzae* type b (13). In our study, *N. meningitidis* was found in 5 (8.3%), *S. pneumoniae* in 15 (31.3%), and *H. influenzae* type b in one (2.1%), and *E. coli* was detected in two (4.2%) infants.

In patients with meningitis, definitive diagnosis is made by microbiological tests. CSF culture, CSF PCR, CSF Gram staining and blood culture are used to determine the causative agent. In the study of Ceyhan et al., culture positivity was found in 23 (18.4%, 16 meningococci, seven pneumococci) out of 125 patients with definite bacterial meningitis, but no information was given about the presence of CSF or blood culture. While all other patients were diagnosed with CSF PCR, the CSF PCR test was found positive in all patients diagnosed with culture (14). In our study, when the agent grown in the CSF culture of patients with bacterial meningitis was examined, *E. coli* was found in two patients, *N. meningitidis* in one patient, and *S. pneumoniae* in eight patients.

Considering the agent reproduced in blood culture, *S. pneumoniae* growth was detected in six of the patients diagnosed with bacterial meningitis.

H. influenzae in one patient, *N. meningitidis* and *S. pneumoniae* in four patients were positive in bacterial meningitis, and CSF PCR test was positive in 14 patients. Three patients with bacterial meningitis with a negative CSF PCR test were diagnosed with growth in CSF culture (two *E. coli* meningitis, one *S. pneumoniae* meningitis). CSF PCR test was also positive in all of the patients with growth in their blood culture. It was observed that the most effective examination in diagnosing bacterial meningitis was CSF PCR examination (Table 3).

Bacterial and enteroviral meningitis can be seen in all ages and sexes. Barseem et al. have conducted a study with 23 boys and 17 girls, a total of 40 children with acute meningitis, and they were aged between four months and 14 years (15).

In the study by Abdallah et al., the age range of 161 children was eight months-13 years, and most of the included patients were males (61.5%) (16). Seventy percent of the 167 children included in the study by Dubos et al. were males [median age= 4.6 years (0.2-14.9)] (17). El Shorbagy et al. reported 40 suspected children were between four months and 14 years of age (15). When we look at similar studies conducted in Türkiye, age distribution and male-dominant results are similar (Table 5). Forty-eight patients were included in our study, and 79% of the patients had acute meningitis, Two of them were males, and median age of the patients was 72 months (one month-18 years).

In meningitis, fever, headache, nausea, and vomiting are the most common complaints at presentation (15,16,18,19). On physical examination, changes in consciousness, menings irritation findings, and focal neurological findings indicate central nervous system infection (18).

In a study covering the data of European countries and in studies conducted in Türkiye, the most common complaints in children with acute meningitis have been found as fever, headache, neck stiffness and vomiting (11-14,19-23).

In terms of complaints and physical examination findings indicating central nervous system involvement, headache at a rate of 58.3%, nuchal rigidity 45.8%, altered consciousness 2.1%, seizure 8.3%, focal neurologic findings 4.2% were observed in children with acute meningitis. Imananagha et al. have found nuchal stiffness in 86 children with meningitis to be 52.6%, brudzinski sign 77.5%, and kerning sign 51.4% positive (24). In a study involving European countries, headache has been reported as 78%, neck stiffness as 40-82%, altered consciousness as 13-51%, seizure as 8.3%, focal neurologic findings as 11-16%, and seizures as 10-25% (11). In studies conducted in Türkiye, headache has been found as 24.8-68.5%, neck stiffness as 43-84%, altered consciousness as 24.6-30%, seizure as 20.7-42.6%, focal neurologic findings as 5-13.9%, and seizure rates as 10-25%. As can be seen, headache and neck stiffness are the most common neurological findings (Table 5).

The gold standard method to distinguish whether meningitis is bacterial or viral in vitro is CSF or blood culture. If the patient used antibiotics before sampling, the chance of growth in the culture decreases. The rate of production of the microorganism in the cultures of patients who did not use antibiotics is between 70-85% (25).

CSF is a body fluid and has many metabolic functions. Glucose, protein, chlorine and many parameters such as other cellular changes, microbial and viral agents are examined in CSF fluid for diagnostic purposes. Decreasing CSF glucose concentration results from bacterial metabolism and is typical in cases of bacterial meningitis. However, it also depends on the blood glucose level measured simultaneously, taking into account the CSF/blood glucose ratio (26). In healthy individuals, protein level in CSF parameter is between 45-50 mg/dL.

CSF protein is slightly elevated (mean 56 mg/dL) in cases of viral meningitis and higher in bacterial meningitis (mean 135 mg/dL). Protein levels above 188 mg/dL in CSF are useful in differentiating between bacterial and viral meningitis.

In the study of Emiroglu et al., CSF protein level and cell number have been found higher in children with meningitis than in children without meningitis (23). In the study of

Table 5. Examples of childhood meningitis studies in Türkiye

	Kara Uzun (20)		Abuhandan (21)	Ceyhan (13,14)		Türel (22)	Emiroğlu (23)	Babayeva
Years	1995-1996	2012-2016	2010-2011	2005-2012	2015-2018	2005-2013	2011-2013	2013-2020
Patient number	54	17	92	645	125	283	101	48
Age (month)	40.5 (1-168)	71.3 (3-204)	50 ± 49 (3-192)	1-216	42	12 (1-60)	24 (1-168)	72 (1-240)
Sex M (%)	29 (53.7)	12 (70.6)	50 (54.3)	1225 (84)		194 (68.6)	62 (61.4)	38 (79.2)
N. meningitidis	52.2%	27.3%	9.2%	51.6%	71%	21%	5.5%	18.2%
S. pneumoniae	26.1%	54.5%	54.3%	30.2%	26.4%	30.3%	61.1%	68.2%
H. influenzae type b	17.4%	9.1%	-	18.1%	2.4%	36.3%	5.5%	4.5%
Fever	27%	23.5%	91.3%	-	-	97%	98.0%	77%
Vomiting	-	-	87%	-	-	93%	46.5%	64.6%
Headache	-	-	68.5%	-	-	-	24.8%	58.3%
Neck rigidity	-	-	60.9%	-	-	84%		45.8%
Seizure	-	23.6%	20.7%	-	-	23%	42.6%	8.3%
Focal neurological finding	-	--	-	-	-	5%	13.9%	4.2%
Clouding of consciousness	-	24.6%	-	-	-	26%	-	2.15%
Rash	-	-	2.2%	-	-	10	-	2.1%

El Shorbagy et al., CSF protein has been found to be significantly higher in children with bacterial meningitis ($p < 0.001$), while CSF sugar has been detected to be significantly lower ($p < 0.001$) (15). Considering the distribution of CSF biological parameters of 96 patients diagnosed with bacterial meningitis by Dubos et al., the authors have concluded a significant increase in CSF protein level (80 mg/dL) and CSF neutrophil count (1000/mm^3) and a significant decrease in glucose value (17). Abuhandan et al. have found that if CSF protein is normal or close to normal and if CSF sugar is close to or below half of the concomitant blood sugar, then this is in favor of aseptic meningitis (21). In the study of Mayah et al., CSF protein has been significantly increased in patients with bacterial meningitis compared to patients with aseptic meningitis ($p < 0.05$), while CSF glucose level has been determined significantly lower in patients with bacterial meningitis compared to patients with aseptic meningitis ($p < 0.05$) (12).

In our study, CSF glucose value was found to be significantly lower in patients with bacterial meningitis compared to patients with enteroviral meningitis ($p= 0.001$), CSF protein was found to be higher ($p= 0.013$), but no difference was observed between the groups in concomitant glucose values ($p= 0.954$).

Normal CSF leukocyte count is <5 to 10 leukocytes/mm^3, consisting mainly of mononuclear cells. In children (≤14 years of age), 321 leukocytes/mm^3 has been determined as the limit for the distinction between bacterial meningitis and viral meningitis (26). Abuhandan et al. have demonstrated that a CSF leukocyte count above 1000/mm^3 and PMNL predominance (>75%), a CSF protein over 100-500 mg/dL (15-45 mg/dL) and a CSF sugar below half of concomitant blood sugar, and the presence of the agent in CSF gram staining or the production of the agent in its culture are in favor of bacterial meningitis, and the presence of leukocytes in CSF between 100-500/mm^3 and lymphocytes predominance (>75%), and no growth in culture demonstrate aseptic meningitis (21).

In different studies, total leukocyte count, neutrophil count, and neutrophil ratio in CSF have also been found to be significantly higher in children with bacterial meningitis (12,15). However, in our study, there was no difference CSF leukocytes, CSF neutrophils, and CSF lymphocytes counts between bacterial meningitis and enteroviral meningitis. This shows the importance of culture and PCR methods in definitive diagnosis.

High acute phase reactants are expected in children with meningitis. In the study of Mayah et al., CRP and PCT values were found to be significantly higher in children with bacterial meningitis compared to children with aseptic meningitis ($p < 0.05$ for both) (12). El Shorbagy et al. have found significantly higher blood CRP and PCT values in children with bacterial meningitis than in children with viral meningitis ($p < 0.001$ for both).

In addition, diagnostic cut-off values were found to be >10 ng/mL for PCT and >20 mg/dL for CRP. PCT concentration >2 ng/mL had 100% sensitivity and negative predictive value for bacterial meningitis, but specificity and positive predictive values were only 63% and 67%, respectively (15). The results of the study conducted by Emiroğlu et al. show that ESR, CRP and PCT levels increase in childhood meningitis, CRP> 22.55 mg/L, ESR> 36.5 mm/hour, and PCT> 6.795 mg/ml indicate bacterial meningitis (23). In the study of Sadarangani et al., it has been reported that determining the CRP level is a useful parameter in the diagnosis of bacterial meningitis (27).

In our study, CRP> 5 mg/dL was found in favor of bacterial meningitis. In our study, only PCT value was found to be significantly higher in patients with bacterial meningitis than in patients with enteroviral meningitis ($p= 0.010$). When the cut-off value of PCT was taken as 0.20, sensitivity was 82.4%, specificity was 80%, PPV was 82.4%, and NPV was 80%. Accordingly, determination of serum CRP and PCT levels is an important biomarker in bacterial-viral differentiation.

In the study of Turel et al., 38% of the patients with meningitis had taken antibiotics before, and 92.6% of them were given antibiotics in the treatment of meningitis (22). Nine (18.8%) of our patients had received antibiotic treatment before admission to the hospital, but the dose and duration could not be determined precisely. Antibiotic treatment was used in all of our patients because the CSF PCR test was not performed immediately.

Computed tomography and magnetic resonance imaging methods may show inflammation in some patients with meningitis. However, the absence of inflammation on imaging does not exclude the absence of meningitis, but it plays an important role in the detection of complications (28). In our study, it was determined that imaging methods were used to determine complications, especially in patients with bacterial meningitis.

In our retrospective study, some data could not be reached due to the deficiencies in the records.

There was a lack of information on the names and doses of the antibiotics used prior to admission. In addition, The duration of the CSF PCR test was influenced by the rate and duration of antibiotic use, and as the duration of the study was highly variable during the study period, the effect could not be determined.

Conclusion

Meningitis is a common infection in childhood. With the introduction of conjugated vaccines into national vaccine schemes, the incidence of acute bacterial meningitis in children is decreasing. However, in terms of the morbidity and mortality observed in bacterial meningitis, prompt diagnosis and early treatment are important. Enteroviral meningitis are diagnosed more with the widespread use of CSF PCR test. Differentiation of bacterial meningitis and viral meningitis prevent inappropriate use of antibiotics. While CSF PCR test seems to be the most effective diagnostic tool in this regard, PCT value in blood is also seen significant. With the immediate study of CSF PCR test, unnecessary antibiotics use may be prevented.

Ethics Committe Approval: Ethics committee approval for the study was obtained from Selçuk University Faculty of Medicine Deanery Local Ethics Committee (Decision no: 2022/364, Date: 23.08.2022).

Informed Consent: Patient consent was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- All of authors; Design- All of authors; Supervision- All of authors; Data Collection and/or Processing- All of authors; Analysis and/or Interpretation- All of authors; Literature Search - AB, ME; Writing- AB, ME, GA; Critical Review- All of authors.

Conflict of Interest: All authors declare that they have no conflicts of interest or funding to disclose.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. *Kim KS. Acute bacterial meningitis in infants and children. Lancet Infect Dis 2010;10(1):32-42. https://doi.org/10.1016/S1473-3099(09)70306-8*
2. *World Health Organization. Bacterial meningitis (including Haemophilus influenzae type b (Hib), Neisseria meningitidis, and Streptococcus pneumoniae). Available from: http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/sentinel/meningit is_surveillance/en/ (Accessed date: 08.03.2019).*
3. *Franco-Paredes C, Lammoglia L, Hernández I, Santos-Preciado JI. Epidemiology and outcomes of bacterial meningitis in Mexican children: 10-year experience (1993-2003). Int J Infect Dis 2008;12(4):380-6. https://doi.org/10.1016/j.ijid.2007.09.012*
4. *Thigpen MC, Whitney CG, Messonnier NE, Zell ER, Lynfield R, Hadler JL, et al. Bacterial meningitis in the United States, 1998-2007. N Engl J Med 2011;364(21):2016-25. https://doi.org/10.1056/NEJMoa1005384*
5. *Redington JJ, Tyler KL. Viral infections of the nervous system, 2002: Update on diagnosis and treatment. Arch Neurol 2002;59(5):712-8. https://doi.org/10.1001/archneur.59.5.712*
6. *Fortnum HM, Davis AC. Epidemiology of bacterial meningitis. Arch Dis Child 1993;68(6):763-7. https://doi.org/10.1136/adc.68.6.763*
7. *Shao PL, Chang LY, Hsieh SM, Chang SC, Pan SC, Lu CY, et al. Safety and immunogenicity of a tetravalent polysaccharide vaccine against meningococcal disease. J Formosan Med Assoc 2009; 108:539-47. https://doi.org/10.1016/S0929-6646(09)60371-5 25.*
8. *Snape MD, Perrett KP, Ford KJ, John TM, Pace D, Yu LM, et al. Immunogenicity of a tetravalent meningococcal glycoconjugate vaccine in infants: A randomized controlled trial. JAMA 2008; 299:173-84. https://doi.org/10.1001/jama.2007.29-c*
9. *Verma R, Fisher MC. Bacterial meningitis vaccines: Not just for kids. Curr Infect Dis Rep 2009;11:302-8. https://doi.org/10.1007/s11908-009-0045-z*
10. *Ceyhan M, Ozsurekci Y, Gürler N, Karadag Oncel E, Camcioglu Y, Salman N, et al. Bacterial agents causing meningitis during 2013-2014 in Turkey: A multi-center hospital-based prospective surveillance study. Hum Vaccin Immunother 2016;12(11):2940-5. https://doi.org/10.1080/21645515.2016.1209278*
11. *van de Beek D, Cabellos C, Dzupova O, Esposito S, Klein M, Kloek AT, et al. ESCMID guideline: Diagnosis and treatment of acute bacterial meningitis. Clin Microbiol Infect 2016;22(Suppl 3):37-62. https://doi.org/10.1016/j.cmi.2016.01.007*
12. *Mayah WW, El-Yamany S, Jiman-Fatani A, El-Saadany S, Hassanien M, Hasan A, et al. Study of different diagnostic markers used to differentiate septic from aseptic meningitis. J Microscopy Ultrastructure 2013; 1:35-42. https://doi.org/10.1016/j.jmau.2013.06.007*
13. *Ceyhan M, Ozsurekci Y, Tanır Basaranoglu S, Gurler N, Sali E, Keser Emiroglu M, et al. Multicenter hospital-based prospective surveillance study of bacterial agents causing meningitis and seroprevalence of different serogroups of neisseria meningitidis, haemophilus influenzae type B, and Streptococcus pneumoniae during 2015 to 2018 in Turkey. mSphere 2020;5(2):e00060-20. https://doi.org/10.1128/ mSphere.00060-20*
14. *Ceyhan M, Gürler N, Ozsurekci Y, Keser M, Aycan AE, Gurbuz V, et al. Meningitis caused by neisseria meningitidis, hemophilus influenzae type B and streptococcus pneumoniae during 2005-2012 in Turkey. A multicenter prospective surveillance study. Hum Vaccin Immunother 2014;10(9):2706-12. https://doi.org/10.4161/hv.29678*
15. *El Shorbagy HH, Barseem NF, Abdelghani WE, Suliman HA, Al-Shokary AH, Elsadek AE, et al. The value of serum procalcitonin in acute meningitis in children. J Clin Neurosci 2018; 56:28-33. https://doi.org/10.1016/j.jocn.2018.08.012*
16. *Abdallah MS, Philemon R, Kadri A, Al-Hinai A, Saajan AM, Gidabayda JG, et al. Prevalence, aetiological agents, and antimicrobial sensitivity pattern of bacterial meningitis among children receiving care at KCMC referral hospital in Tanzania. East Afr Health Res J 2018;2(1):1-9*
17. *Dubos F, Korczowski B, Aygun DA, Martinot A, Prat C, Galetto-Lacour A, et al. Serum procalcitonin level and other biological markers to distinguish between bacterial and aseptic meningitis in children: A European multicenter case cohort study. Arch Pediatr Adolesc Med 2008;162(12):1157-63. https://doi.org/10.1001/archpedi.162.12.1157*
18. *Kanra G, Ceyhan M, Kara A. Menenjit II: Klinik bulgular ve tanı. Çocuk Sağlığı Hastalıkları Derg 2003;46:128-38. 13.*
19. *Tebruegge M, Curtis N. Epidemiology, etiology, pathogenesis, and diagnosis of recurrent bacterial meningitis. Clin Microbiol Rev 2008;21(3):519-37. https://doi.org/10.1128/CMR.00009-08*
20. *Uzun AK, Yöney A, Kunak B, Yüksek SK, Tezer H. Ülkemizde çocuklarda iki farklı zaman diliminde izlenen akut bakteriyel menenjitlerin değerlendirilmesi. Türkiye Çocuk Hastalıkları Derg 2018;12:193-9. 9.*
21. *Abuhandan M, Çalik M, Oymak Y, Almaz V, Kaya C, Eren E, et al. Çocuklarda menenjit: 92 olgunun değerlendirilmesi. Dicle Tıp Derg 2013; 40:15-20. https://doi.org/10.5798/diclemedj.0921.2013.01.0217 10.*
22. *Türel Ö, Yildirim C, Yılmaz Y, Akdaş F, Külekçi S, Bakir M. Clinical characteristics and prognostic factors in childhood bacterial meningitis: A multicenter study. Balkan Med J 2013; 2013:80-4. https://doi.org/10.5152/balkanmedj.2012.092 11.*
23. *Emiroglu M, Kesli R, Kilicaslan M. Diagnostic value of clinical and laboratory findings in childhood meningitis. J Pediatric Infect Dis 2020; 15:79-85.*

24. *Imananagha KK, Peters EJ, Philip-Ephraim EE, Ekott JU, Imananagha LN, Ekure EN, et al. Acute bacterial meningitis in a developing country: Diagnosis related mortality among paediatric patients. Cent Afr J Med 1998;44(1):11-5.*

25. *Bijlsma MW, Brouwer MC, Kasanmoentalib ES, Kloek AT, Lucas MJ, Tanck MW, et al. Community-acquired bacterial meningitis in adults in the Netherlands, 2006-14: A prospective cohort study. Lancet Infect Dis 2016;16(3):339-47. https://doi.org/10.1016/S1473-3099(15)00430-2*

26. *Julián-Jiménez A, Morales-Casado M. Usefulness of blood and cerebrospinal fluid laboratory testing to predict bacterial meningitis in the emergency department. Neurología (English Edition) 2019; 34:105-13. https://doi.org/10.1016/j.nrleng.2018.05.005*

27. *Sadarangani M, Willis L, Kadambari S, Gormley S, Young Z, Beckley R, et al. Childhood meningitis in the conjugate vaccine era: A prospective cohort study. Arch Dis Child 2015;100(3):292-4. https://doi.org/10.1136/archdischild-2014-306813*

28. *Saberi A, Roudbary SA, Ghayeghran A, Kazemi S, Hosseininezhad M. Diagnosis of meningitis caused by pathogenic microorganisms using magnetic resonance imaging: A systematic review. Basic Clin Neurosci 2018;9(2):73-86*