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ORIGINAL ARTICLE

Analysis of clinical outcomes in pediatric bacterial meningitis focusing on patients without cerebrospinal fluid pleocytosis

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Background: Cerebrospinal fluid (CSF) cell count and biochemical examinations and cultures form the basis for the diagnosis of bacterial meningitis. However, some patients do not have typical findings and are at a higher risk of being missed or having delayed treatment. To better understand the correlation between CSF results and outcomes, we evaluated CSF data focusing on the patients with atypical findings.
Methods: This study enrolled CSF culture-proven bacterial meningitis patients aged from 1 month to 18 years in a medical center. The patients were divided into "normal" and "abnormal" groups for each laboratory result and in combination. The correlations between the laboratory results and the outcomes were analyzed.
Results: A total of 175 children with confirmed bacterial meningitis were enrolled. In CSF examinations, 16.2% of patients had normal white blood cell counts, 29.5% had normal glucose levels, 24.5% had normal protein levels, 10.2% had normal results in two items, and 8.6% had normal results in all three items. In logistic regression analysis, a normal CSF leukocyte count and increased CSF protein level were related to poor outcomes. Patients with meningitis caused by *Streptococcus pneumoniae* and hyponatremia were at a higher risk of mortality and the development of sequelae.
Conclusions: In children with bacterial meningitis, nontypical CSF findings and, in particular, normal CSF leukocyte count and increased protein level may indicate a worse prognosis.

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Introduction

Bacterial meningitis continues to be a leading cause of mortality and morbidity in children despite the development of new medications.[1–3] Patients suspected of having bacterial meningitis remain a clinical emergency requiring an immediate diagnosis and early treatment. Cerebrospinal fluid (CSF) cell count and biochemical examinations and cultures are fundamental laboratory examinations for making a diagnosis. Typical CSF findings among adult patients are elevated white blood cell (WBC) count ($>1000 \times 10^6$/L and >50% polymorphonuclear leukocytes), decreased glucose level (<2.2 mmol/L), and increased protein concentration (>1 g/L).[4] Nigrovic et al[5–7] proposed the Bacterial Meningitis Score which classifies children at very low risk of bacterial meningitis if they lack all of the following criteria: positive CSF Gram stain, CSF protein level greater than 0.8 g/L, CSF absolute neutrophil count greater than 1000×10^6/L, peripheral absolute neutrophil count greater than 10×10^9/L, and a history of seizures before or at the time of presentation. The score has good sensitivity and specificity to identify bacterial meningitis in children with CSF pleocytosis. However, some patients do not have typical laboratory findings or CSF pleocytosis. The patients with atypical laboratory findings are at a higher risk of being missed or of experiencing a delay in receiving appropriate treatment, which increases the risk of a poor prognosis.[8–10] In order to understand the correlation between CSF results and outcomes, we evaluated CSF data and outcomes of patients with culture-proven bacterial meningitis. We focused on children with bacterial meningitis without abnormal CSF laboratory findings. Our main purpose was to identify the risk factors for poor outcomes, so that clinicians are alert while treating patients who may be easily missed but are actually at a high risk of mortality and morbidity.

Methods

This study was conducted in a tertiary medical center in northern Taiwan. A database was created to record the children with meningitis. We selected patients from a registry database, and enrolled all patients with the diagnosis of culture-proven bacterial meningitis aged from 1 month to 18 years, from January 1984 to December 2012. We collected demographic information and laboratory findings by retrospective chart review. Laboratory findings included WBC count, glucose levels, sodium levels, total protein levels, and CSF and blood culture results. Age, sex, treatment, complications, and outcomes were also recorded for analysis.

In patients suspected of having meningitis, lumbar punctures and blood tests were performed on admission before initiating antibiotic treatment. Routine laboratory examinations included CSF cell count, biochemical examinations and cultures, and blood cell count and cultures. Serum sodium and glucose levels were reviewed in most patients but were not part of routine examinations. The CSF-to-serum glucose ratio was calculated in patients with available data. We excluded children diagnosed with bacterial meningitis without bacteria isolated from the CSF or whose CSF cultures yielded normal skin flora (e.g., coagulase-negative staphylococci) and clinical presentation suggested contamination. We also excluded patients with congenital infections. Some patients had traumatic lumbar punctures or poor sample collection, and their CSF WBC count, glucose, or protein data were excluded. If a patient had multiple laboratory results, we registered only the first in each episode. For those with recurrent meningitis, the laboratory findings in each episode were separately calculated.

The patients were divided into infants (age: 1 month to <1 year) and children (age $\geq$ 1 year). We defined a normal CSF WBC count as 20×10^6/L or less in all patients; a normal CSF protein level was defined as 1 g/L or less in infants and 0.5 g/L or less in the children. A normal CSF glucose level was defined as 2.2 mmol/L or greater, a normal CSF-to-serum glucose ratio as 0.6 or greater, a normal serum sodium level as 130 mmol/L or greater, and a normal serum WBC count as between 4.5×10^9/L and 11×10^9/L in all patients.

The outcomes were divided into "death or sequelae", "recovery", and "lost to follow up". Sequelae were defined as physical or psychological morbidities lasting longer than 6 months after the meningitis episode, including mental retardation, cerebral palsy, ataxia, hearing impairment, and epilepsy. Lost to follow up was defined as an inability to reach the patient at 6 months after the meningitis episode. We excluded those patients who were lost to follow up from outcome analysis. The patients who died or had sequelae were classified into the poor outcome group, and those who were followed up and recovered without sequelae into the good outcome group.

Statistical analysis

In each single laboratory item or combined items, patient outcomes were compared using the Chi-square test, Fisher's exact test, or one-way analysis of variance. We further analyzed the outcomes of patients with different CSF WBC count results and those with normal CSF WBC count results. For identifying the relationships between different items, we used logistic regression to define the strongest outcome predictors. The threshold of statistical significance was set at $p < 0.05$. Statistical analyses were performed using SPSS version 12.0 (SPSS, Inc., Chicago, IL, USA).

Results

This study enrolled 175 patients between 1 month and 18 years of age with culture-proven meningitis, including 64 girls (36.6%) and 111 boys (63.4%). The age distribution of the patients is shown in Fig. 1. A total of 107 patients (61.1%) were aged 1 month to less than 1 year and were classified as infants. Twenty-one patients (12.0%) were lost to follow up, 81 (46.3%) recovered without sequelae (good outcome group), and 73 (41.7%) died or had sequelae (poor outcome group).

Laboratory results

The laboratory findings are listed in Table 1. In CSF examinations, 16.2% of patients had a normal WBC count, 29.5% had a normal glucose level, 24.5% had a normal protein level, and 88.8% had a normal CSF-to-serum glucose ratio. Approximately one third of the patients (31.8%) had a normal blood WBC count, and hyponatremia was noted in 13.2% of the examined patients.

The correlations between laboratory findings and outcomes are listed in Table 2. The patients with increased CSF total protein concentration [odds ratio (OR): 3.26; 95% confidence interval (CI): 1.34–7.94, $p = 0.007$], hyponatremia (OR: 3.81; 95% CI: 1.00–14.48, $p = 0.04$), and *Streptococcus pneumoniae* infections (OR: 2.68; 95% CI: 1.30–5.50, $p = 0.007$) were associated with a poor outcome in univariate analysis. In multivariate analysis, the indicators most closely related to a poor outcome were normal CSF WBC count (OR: 7.42; 95% CI: 1.18–46.69, $p = 0.03$) and increased CSF total protein level (OR: 4.85; 95% CI: 1.22–19.28 $p = 0.03$). When the patients were divided into several groups according to CSF WBC count, those with a WBC count of 20×10^6/L or less or greater than 5000×10^6/L had worse outcomes (Table 3).

Based on combinations of the following three CSF laboratory examinations, the patients were subdivided into eight groups: WBC count, glucose levels, and protein levels (Table 4). Among 128 patients with complete information on these three items without traumatic tap, only 53.1% (68/128) had typical meningitis findings with increased WBC count, decreased glucose, and increased protein levels. Twenty-four patients (18.8%) had normal laboratory findings on at least two items and 11 patients (8.6%) had laboratory findings within normal limits in all three CSF items. Eight patients (6.3%) with an increased WBC count, but normal glucose and protein levels had the best outcomes, and all recovered without sequelae. The worst outcome groups were those with a normal CSF WBC count and abnormal CSF biochemical results, with 75–100% morbidity and mortality rates. We further analyzed the relationship between CSF and blood WBC counts by Chi-square test. A correlation was found between CSF WBC count of 20×10^6/L or less and blood WBC count of 4000×10^6/L or less ($p = 0.029$).

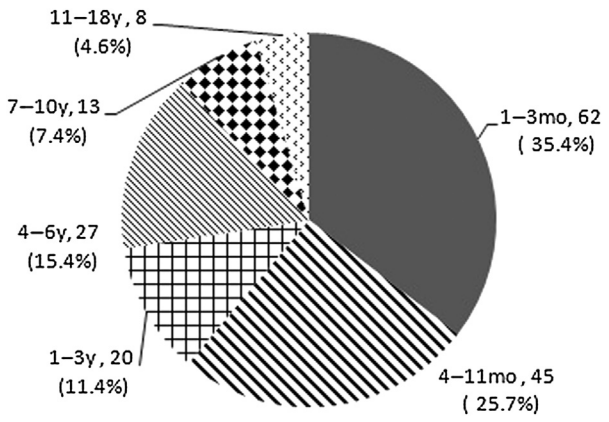

Figure 1. Age distribution of 175 pediatric patients with bacterial meningitis.

Table 1 Laboratory findings of children with bacterial meningitis[a]

Laboratory item	Normal result		Abnormal result		Total patient no.
	Patient no.	(%)	Patient no.	(%)	
CSF WBC count	25	16.2	129	83.8	154
CSF glucose level	43	29.5	103	70.5	146
CSF protein level	36	24.5	111	75.5	147
CSF/serum glucose ratio	95	88.8	12	11.2	107
Blood WBC count	55	31.8	118	68.2	173
Serum sodium level	112	86.8	17	13.2	129

[a] Some laboratory data were not checked or were eliminated due to traumatic tapping in some patients.
CSF = cerebrospinal fluid; WBC = white blood cell.

Culture results

The most commonly isolated pathogens were *S. pneumoniae* (51 episodes, 29.1%), followed by *Haemophilus influenzae* type b (23 episodes, 13.1%), *Escherichia coli* (16 episodes, 9.1%), and *Streptococcus agalactiae* (15 episodes, 8.6%). Other Gram-positive bacteria (38 episodes, 21.7%) isolated were *Streptococcus pyogenes, Neisseria meningitidis,* coagulase-negative *Staphylococcus, Enterococcus, Staphylococcus aureus, Streptococcus bovis, and Streptococcus sanguinis.* Gram-negative bacteria (32 episodes, 18.3%) isolated were *Enterobacter cloacae, Klebsiella pneumoniae, Alcaligenes, Plesiomonas, Pseudomonas aeruginosa, Salmonella, Haemophilus parainfluenzae,* and *Elizabethkingia meningoseptica*. Patients with *S. pneumoniae* meningitis had the worst outcomes; 64.4% died or had sequelae. By contrast, patients infected by other Gram-positive bacteria had the best outcomes with 83.4% achieving total recovery. Other Gram-negative bacteria had relatively bad outcomes with 60% morbidity and mortality rates (Fig. 2).

Discussion

Typical CSF findings in meningitis patients are elevated WBC count, decreased glucose concentrations, and increased protein concentrations; however, these findings were only present in 54.6% of our patients. Our results showed that low CSF WBC count correlated with poor outcomes of the pediatric patients with bacterial meningitis. These patients are at a high risk of being missed or having

Table 2 Correlation between laboratory findings and poor outcomes with logistic regression analysis

Laboratory item		Poor outcome		Good outcome		Univariate analysis		Multivariate analysis	
		Patient no.	(%)	Patient no.	(%)	*p*	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)
CSF WBC count	Normal	11	55.0	9	45.0	0.36	1.54 (0.61–3.84)	0.03*	7.42 (1.18–46.69)
	Increased	51	34.9	95	65.1				
CSF glucose level	Normal	16	40.0	24	60.0	0.49	1.31 (0.61–2.79)	0.20	2.59 (0.60–11.16)
	Decreased	41	46.6	47	53.4				
CSF protein level	Normal	8	24.2	25	75.8	0.007*	3.26 (1.34–7.94)	0.03*	4.85 (1.22–19.28)
	Increased	49	51.0	47	49.0				
CSF/serum glucose ratio	≥0.6	6	54.5	5	45.5	0.75	0.81 (0.23–2.87)	0.11	0.18 (0.02–1.48)
	<0.6	42	49.4	43	50.6				
Blood WBC count	Normal	19	40.4	28	59.6	0.30	1.45 (0.72–2.90)	0.08	3.01 (0.88–10.30)
	Increased	52	49.5	53	50.5				
Serum sodium level	Normal	50	49.0	52	51.0	0.04*	3.81 (1.00–14.48)	0.13	5.41 (0.61–47.86)
	Decreased	11	78.6	3	21.4				
CSF culture	Other pathogens	44	40.4	65	59.6	0.007*	2.68 (1.30–5.50)	0.18	2.19 (0.70–6.83)
	Streptococcus pneumoniae	29	64.4	16	35.6				

CI = confidence interval; CSF = cerebrospinal fluid; WBC = white blood cell.
* Statistical significance.

delayed treatment, and as such increased attention should be paid to these patients in daily clinical practice.

The definition of a normal CSF value varies widely between age groups and among different studies. Studies using a CSF WBC count greater than 21 $\times$ 10^6/L as the diagnostic criterion for neonatal meningitis have shown acceptable sensitivity and specificity[11,12]; however, no specific data for patients aged between 2 months and 18 years are available. Therefore, we defined a normal CSF WBC count as 20 $\times$ 10^6/L or less in infants, and we combined a normal CSF WBC count ($\leq$5 $\times$ 10^6/L, according to the adult criterion) and low pleocytosis (6–20 $\times$ 10^6/L) as the definition of a normal WBC count in the children.[13,14] The reported normal range for CSF protein also varies widely, from 0.15–1.7 g/L among newborns to 0.15–0.5 g/L in adults,[4] whereas a reported normal CSF glucose level varies less among different age groups. A review article reported that the 5th to 95th percentile levels are 1.7–5.6 mmol/L in infants aged 1–2 months, 1.9–4.9 mmol/L in infants aged 2–6 months, 2.4–4.9 mmol/L in infants aged 6–12 months, and 2.8–4.4 mmol/L in adults.[15] For statistical analysis, the normal ranges of the CSF biochemical results in this study were modified from the aforementioned reports.

Table 3 Correlation between CSF WBC count and outcome

CSF WBC count ($\times$ 10^6/L)	Poor outcome		Good outcome	
	Patient no.	(%)	Patient no.	(%)
≤5	7	50.0	7	50.0
6–20	5	62.5	3	37.5
21–100	9	45.0	11	55.0
101–1000	24	46.2	28	53.8
1–5000	9	33.3	18	66.7
>5000	8	53.3	7	46.7

CSF = cerebrospinal fluid; WBC = white blood cell.

Besides age, several other factors can influence laboratory findings, further complicating the interpretation. A delay in analyzing CSF culture findings can result in a decrease in WBC count and glucose level.[16] A lumbar puncture performed after parenteral antibiotics, even if only after a few hours, can lead to negative CSF culture findings.[8] Most single CSF parameters are therefore not efficient in differentiating bacterial meningitis from viral meningitis.[17,18] Evidence from adult meningitis patients suggests that CSF lactate level and serum procalcitonin level would be better discriminative parameters for bacterial meningitis, however, the cost of both examinations limits their availability.[5,19,20]

The current study concentrated on basic CSF and blood examinations that can be carried out in ordinary laboratories, even in laboratories in remote rural areas. The results showed that a low CSF WBC count with increased protein levels and/or decreased glucose levels correlated with poor outcomes of the pediatric patients with bacterial meningitis. While a CSF WBC count of 20 $\times$ 10^6/L or less was a predictor of a poor outcome, a CSF WBC count greater than 5000 $\times$ 10^6/L was also an independent risk factor for a bad prognosis. Previous studies have shown a similar trend in different age groups and specific pathogens. In neonatal bacterial meningitis, a CSF protein level greater than 5 g/L has been reported to be associated with a poor outcome.[21] A CSF WBC count less than 20 $\times$ 10^6/L and a low CSF glucose level have been reported to be correlated to a higher mortality rate among children with pneumococcal meningitis.[22] In a prospective study, Namani et al[23] reported that an increased CSF protein concentration was associated with an increased risk of neurological complications, and that pleocytosis greater than 5000 $\times$ 10^6/L and a CSF-to-blood glucose ratio less than 0.2 also showed the same trend albeit without statistical

Table 4 Outcome of pediatric patients with bacterial meningitis with different CSF laboratory results

CSF items			Poor outcome		Good outcome		Total patient no.
WBC	Glucose	Protein	Patient no.	(%)	Patient no.	(%)	
N	N	N	4	36.4	7	63.6	11
N	N	↑	3	75.0[a]	1	25.0	4
N	↓	N	1	100.0[a]	0	0.0	1
N	↓	↑	4	66.7[a]	2	33.3	6
↑	N	N	0	0.0	8	100.0	8
↑	N	↑	9	52.9	8	47.1	17
↑	↓	N	3	23.1	10	76.9	13
↑	↓	↑	33	48.5	35	51.5	68

[a] Worst outcome groups were those with normal CSF WBC counts and abnormal CSF biochemical results.
CSF = cerebrospinal fluid; N = normal; WBC = white blood cell; ↑ = increased; ↓ = decreased.

significance. Possible explanations are that higher bacteria intensity results in more glucose consumption and more severe inflammation presenting as an increased protein level. The production of cytokines and proinflammatory molecules leads to attraction and activation of leukocytes and the production of reactive oxygen species. Cellular dysfunction such as decreased aggregation or failure to phagocytize would result in poor infection control.[24] A recent study on the pathophysiology of sepsis showed that neutrophil hyperactivity is a critical component of the innate immune response to infectious challenge. In addition, patients with neutropenia or neutrophil dysfunction, regardless of the cause, are at a higher risk of developing infectious complications.[25] In our study, a normal CSF WBC count correlated with neutropenia. Therefore, the lower CSF WBC count may indicate poor host immunity with an inadequate response, leading to poor outcomes.

Hyponatremia is the other independent predictor for a poor prognosis. In contrast to adult meningitis patients in whom hyponatremia is common and benign, we found a correlation between hyponatremia and an increased risk of death or sequelae. In a study by Brouwer et al[26] on adult meningitis, the patients with hyponatremia had an exceptionally high proportion of *Listeria monocytogenes* (73%) infections which may have been a confounding factor, and was associated with mild disease and prolonged duration. In our study, the hyponatremia group had a similar bacteria profile compared with the whole group of patients, with approximately 30% caused by *S. pneumoniae* infections and 45% by Gram-negative bacteria. This distribution of pathogens is quite different from adult data. The possible mechanisms of hyponatremia are inappropriate antidiuretic hormone secretion, cerebral salt-wasting syndrome, and aggressive fluid resuscitation. All of these problems may contribute to a worse prognosis. Treatment options are intravenous maintenance fluids and restricted fluid intake; however, the Cochrane review showed little evidence to support the option.[27]

This study is based on children with culture-confirmed bacterial meningitis. Although we did not include healthy controls for comparisons, we believe our findings are useful to serve as a reminder not to exclude bacterial meningitis according to normal initial CSF examination results, and especially the WBC count.

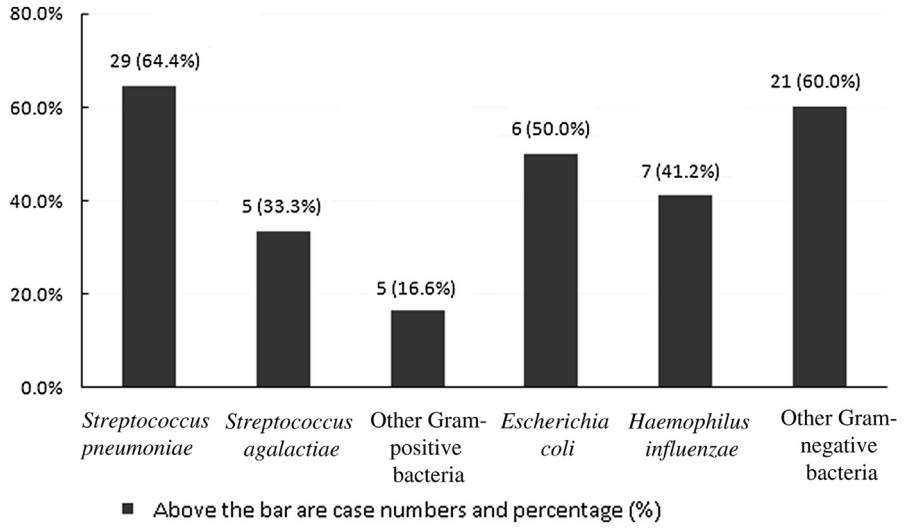

Figure 2. Percentage of poor outcomes of pediatric patients with bacterial meningitis caused by different pathogens.

Conflicts of interest

All authors have no conflicts of interest to disclose.

References

1. Kim KS. Acute bacterial meningitis in infants and children. *Lancet Infect Dis* 2010;**10**:32—42.
2. Chang CJ, Chang WN, Huang LT, Huang SC, Chang YC, Hung PL, et al. Bacterial meningitis in infants: the epidemiology, clinical features, and prognostic factors. *Brain Dev* 2004;**26**:168—75.
3. de Louvois J, Halket S, Harvey D. Neonatal meningitis in England and Wales: sequelae at 5 years of age. *Eur J Pediatr* 2005;**164**:730—4.
4. Gray LD, Fedorko DP. Laboratory diagnosis of bacterial meningitis. *Clin Microbiol Rev* 1992;**5**:130—45.
5. Nigrovic LE, Kuppermann N, Malley R. Development and validation of a multivariable predictive model to distinguish bacterial from aseptic meningitis in children in the post-*Haemophilus influenzae* era. *Pediatrics* 2002;**110**:712—9.
6. Nigrovic LE, Malley R, Kuppermann N. Meta-analysis of bacterial meningitis score validation studies. *Arch Dis Child* 2012;**97**:799—805.
7. Nigrovic LE, Kuppermann N, Macias CG, Cannavino CR, Moro-Sutherland DM, Schremmer RD, et al. Clinical prediction rule for identifying children with cerebrospinal fluid pleocytosis at very low risk of bacterial meningitis. *JAMA* 2007;**297**:52—60.
8. Kanegaye JT, Soliemanzadeh P, Bradley JS. Lumbar puncture in pediatric bacterial meningitis: defining the time interval for recovery of cerebrospinal fluid pathogens after parenteral antibiotic pretreatment. *Pediatrics* 2001;**108**:1169—74.
9. Miner JR, Heegaard W, Mapes A, Biros M. Presentation, time to antibiotics, and mortality of patients with bacterial meningitis at an urban county medical center. *J Emerg Med* 2001;**21**:387—92.
10. Proulx N, Fréchette D, Toye B, Chan J, Kravcik S. Delays in the administration of antibiotics are associated with mortality from adult acute bacterial meningitis. *QJM* 2005;**98**:291—8.
11. Kestenbaum LA, Ebberson J, Zorc JJ, Hodinka RL, Shah SS. Defining cerebrospinal fluid white blood cell count reference values in neonates and young infants. *Pediatrics* 2010;**125**:257—64.
12. Garges HP, Moody MA, Cotten CM, Smith PB, Tiffany KF, Lenfestey R, et al. Neonatal meningitis: what is the correlation among cerebrospinal fluid cultures, blood cultures, and cerebrospinal fluid parameters? *Pediatrics* 2006;**117**:1094—100.
13. Smith SV, Forman DT. Laboratory analysis of cerebrospinal fluid. *Clin Lab Sci* 1994;**7**:32—8.
14. Straus SE, Thorpe KE, Holroyd-Leduc J. How do I perform a lumbar puncture and analyze the results to diagnose bacterial meningitis? *JAMA* 2006;**296**:2012—22.
15. Leen WG, Willemsen MA, Wevers RA, Verbeek MM. Cerebrospinal fluid glucose and lactate: age-specific reference values and implications for clinical practice. *PloS One* 2012;**7**:e42745.
16. Rajesh NT, Dutta S, Prasad R, Narang A. Effect of delay in analysis on neonatal cerebrospinal fluid parameters. *Arch Dis Child Fetal Neonatal Ed* 2010;**95**:F25—9.
17. Ray P, Badarou-Acossi G, Viallon A, Boutoille D, Arthaud M, Trystram D, et al. Accuracy of the cerebrospinal fluid results to differentiate bacterial from non bacterial meningitis, in case of negative Gram-stained smear. *Am J Emerg Med* 2007;**25**:179—84.
18. Bonsu BK, Harper MB. Differentiating acute bacterial meningitis from acute viral meningitis among children with cerebrospinal fluid pleocytosis: a multivariable regression model. *Pediatr Infect Dis J* 2004;**23**:511—7.
19. Viallon A, Desseigne N, Marjollet O, Birynczyk A, Belin M, Guyomarch S, et al. Meningitis in adult patients with a negative direct cerebrospinal fluid examination: value of cytochemical markers for differential diagnosis. *Crit Care* 2011;**15**:R136.
20. Dubos F, Korczowski B, Aygun DA, Martinot A, Prat C, Galetto-Lacour A, et al. Distinguishing between bacterial and aseptic meningitis in children: European comparison of two clinical decision rules. *Arch Dis Child* 2010;**95**:963—7.
21. Lin MC, Chi H, Chiu NC, Huang FY, Ho CS. Factors for poor prognosis of neonatal bacterial meningitis in a medical center in Northern Taiwan. *J Microbiol Immunol Infect* 2012;**45**:442—7.
22. Chao YN, Chiu NC, Huang FY. Clinical features and prognostic factors in childhood pneumococcal meningitis. *J Microbiol Immunol Infect* 2008;**41**:48—53.
23. Namani S, Milenković Z, Koci B. A prospective study of risk factors for neurological complications in childhood bacterial meningitis. *J Pediatr (Rio J)* 2013;**89**:256—62.
24. Barichello T, Fagundes GD, Generoso JS, Elias SG, Simões LR, Teixeira AL. Pathophysiology of neonatal acute bacterial meningitis. *J Med Microbiol* 2013;**62**:1781—9.
25. Remick DG. Pathophysiology of sepsis. *Am J Pathol* 2007;**170**:1435—44.
26. Brouwer MC, van de Beek D, Heckenberg SG, Spanjaard L, de Gans J. Hyponatraemia in adults with community-acquired bacterial meningitis. *QJM* 2007;**100**:37—40.
27. Maconochie IK, Bhaumik S. Fluid therapy for acute bacterial meningitis. *Cochrane Database Syst Rev* 2014;**5**:CD004786.