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COMMUNITY-ACQUIRED BACTERIAL MENINGITIS IN ADULTS: ANTIBIOTIC TIMING IN DISEASE COURSE AND OUTCOME

Running title: Bacterial meningitis and antibiotic timing in adults

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None.

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Both authors planned, wrote, reviewed and revised the article and approved the final version of the manuscript. Dr Lepur was primarily responsible for data collection and basic statistics. Prof Baršić performed advanced statistical tests.

ABSTRACT

Objectives

Despite improvements in diagnostic and therapeutic approach to adult patients with bacterial meningitis, the overall mortality rate is still high. The aim of this study was to evaluate antibiotic timing in the course and outcome of bacterial meningitis..

Methods

Two hundred and eighty six patients with community-acquired bacterial meningitis aged 14 years and more were included in this retrospective cohort study. Observational period was between 1 January 1990 and 31 December 2004. To assess the association of antibiotic timing and disease outcome we analyzed three timing periods (according to the onset of disease, onset of consciousness disturbance and the time of admission to hospital). Analysis was also performed in a subgroup of culture positive meningitis in 176 patients with altered mental status.

Results

Unfavorable outcome was found in 125 (43,7%) patients. In this group, the start of appropriate antibiotic treatment in relation to the onset of first symptoms and particularly to the onset of consciousness disturbance was significantly delayed ($p=0,018$ and $p<0,001$ respectively) compared to the favorable group. Logistic regression analysis in a subgroup of culture positive meningitis in patients with altered mental status revealed that early adequate antibiotic treatment related to the onset of overt signs of meningitis was independently associated with favorable outcome (OR= 11,19; 95% CI 4,37-32,57; $p<0,001$). Advanced age, lower GCS and seizures (OR=1.05, OR=1,45 and OR= 3.65, respectively) were other risk factors of poor outcome. The presence of chronic diseases, pneumococcal etiology and clinical and laboratory variables which are indicators of disease severity (renal and/or liver

dysfunction, hypotension and low cerebrospinal fluid glucose) were not confirmed as independent risk factors of poor outcome.

Conclusions

Our study emphasizes the importance of early and adequate antibiotic treatment in the management of bacterial meningitis which significantly enhances the chances for favorable outcome.

INTRODUCTION

Despite advances in the treatment of severe infections, particularly associated with critical care medicine, many patients with bacterial meningitis have unfavorable outcome. Except for proved benefit from adjunctive corticosteroid treatment, particularly in pneumococcal disease, there are no significant improvements in diagnostic and therapeutic approach to adult patients with bacterial meningitis (1-4). The overall mortality rate before the routine use of dexamethasone was high, up to 28%, in pneumococcal meningitis even up to 37% (4-11). A large number of survivors suffer from long-term neurological sequelae (4). Various prognostic factors associated with adverse clinical outcome were reported so far (6-9,12,13). The most common factors independently associated with unfavorable outcome were APACHE II score >13, hypotension, seizures, obtunded mental state on admission, age over 60 years and pneumococcal etiology (8,9,13,14). It is reasonable to believe that treatment outcome could be improved by timely and appropriate antibiotic therapy. Various recent studies have tried to assess the role of antibiotic timing in disease outcome, but final evidence is still lacking (5,12).

The aim of this study was to evaluate antibiotic timing in the course of bacterial meningitis and outcome of the disease.

PATIENTS AND METHODS

Data collection

The study was performed at the Zagreb Hospital for Infectious Diseases, a tertiary care, university-affiliated teaching hospital with 320 beds. The patients were identified through the hospital's computerized data system based on diagnosis at discharge. The original written patient medical records were used to collect the data. The following parameters were recorded: age, gender, co-existing diseases, presenting symptoms, physical and neurological signs, cerebrospinal fluid (CSF) characteristics, laboratory results on admission, microbiological findings in CSF and blood, clinical outcome, treatment and timing of adequate antibiotic related to the onset of disease, the onset of consciousness disturbance and the time of admission to hospital. We constructed a computerized database that included all patients discharged from our hospital with a diagnosis of bacterial meningitis between 1 January 1990 to 31 December 2004. Microsoft Access 2002 software was used to create the database.

Patients' selection

A total of 353 first episodes of bacterial meningitis were treated in our hospital in the fifteen-year observational period. One hundred and seventy patients were excluded from the study because of age below 14 years (20 patients), presence of brain abscess or subdural empyema (17 patients), meningitis limited to the spinal area (4 patients), nosocomial and shunt meningitis (126 patients) and certain reasons not associated with bacterial meningitis (3 patients who died of pulmonary embolism, myocardial infarction and renal failure, respectively).

Antibiotic timing could not be determined in 67 patients who were also excluded from the analysis. In order to test possible selection bias, a bivariate analysis was performed and showed no differences in relevant demographic and clinical variables (outcome, age, etiology,

mechanical ventilation, duration of hospitalization and administration of corticosteroids) between these and the remaining patients. Overall, 286 patients remained in the study to test the association of antibiotic timing and disease outcome. Further analysis was also performed in a subgroup of culture positive meningitis in patients with altered mental status.

Definitions

Bacterial meningitis was diagnosed on the basis of a compatible clinical picture and a positive CSF culture; or a negative CSF culture with a positive CSF bacterial antigen test; or a positive blood culture; or a positive Gram stain of a CSF sample. A culture negative bacterial meningitis was diagnosed on the basis of a compatible clinical picture, neutrophilic pleocytosis (≥ 10 white cells/ml of CSF with more than 50% neutrophils), CSF-blood glucose ratio <0,4 and CSF protein concentration >0,450 g/l. Bacterial meningitis was considered community-acquired if the patients had never been previously hospitalized or the onset of the disease occurred 2 weeks after discharging from hospital or 4 weeks after a surgical treatment (8).

Mental status was assessed using the Glasgow Coma Scale score (GCS) and the recorded scores were the worst during 24 hours after admission to the hospital because of greater validity, to our opinion, in estimating disease severity (15). Altered mental status was defined as GCS < 15. The onset times of first symptoms and consciousness disturbance were obtained from housemates during medical history taking. The onset of disease was defined with first, nonspecific symptoms (fever, headache, malaise, vomiting). Focal neurological deficit was defined as aphasia, cranial-nerve palsy, monoparesis or hemiparesis on admission. Hypotension was defined as mean arterial pressure (MAP) < 70 mmHg.

Appropriate therapy was defined as a regimen to which one or more of the bacteria isolated at baseline were sensitive, administered in adequate doses and which penetrates well into the CSF. The timing of appropriate antibacterial treatment was assessed regarding the

onset of the disease, the onset of consciousness disturbance and the time of admission to hospital.

The majority of patients received empirical therapy with ceftriaxone alone (80/286; 27,9%) or in combination with ampicillin, followed with penicillin G-sodium (55/286; 19,2%) and cefotaxime (27/286; 9,4%). Diverse combinations of antibiotics were used in 99 patients (34,6%).

Underlying medical condition(s) were classified according to the modified criteria by Knaus (16): A) no known underlying diseases, B) presence of mild chronic diseases with slight functional limitation, C) severe chronic diseases with severe limitation, requiring constant medical surveillance, D) bed-ridden patients in terminal stages of underlying diseases (e.g. severe dementia, malignant diseases with metastases, decompensated liver cirrhosis etc.).

Renal lesion on admission was defined as increased creatinine concentration above the upper limit of the normal range. Liver lesion was defined as increased bilirubin and/or aminotransferases levels above the upper limit of the normal range.

The patients were stratified into two groups according to disease outcome: favorable and unfavorable. The patients' clinical outcome was assessed by using the Glasgow Outcome Scale score (GOS) at the time of discharge from the hospital (17). Unfavorable clinical outcomes included death (GOS 1), vegetative state (GOS 2), severe neurological deficit (GOS 3) and moderate disability (GOS 4). GOS 5 (mild or no disability) was considered a favorable outcome.

Statistical analysis

Univariate statistics included calculation of mean value, standard deviation, median and interquartiles for continuous variables. Values for categorical variables were presented as frequencies. The primary outcome variable was the Glasgow Outcome Score. Bivariate statistics assessed the differences between favorable and unfavorable groups. All relevant

demographic, clinical and laboratory variables of both groups were compared. To contrast the quantitative variables, nonparametric Mann-Whitney's test was used. For categorical data the chi-square test and the Fisher's exact test when appropriate, were used. Logistic regression analysis was performed to ascertain the independent predictive potential of antibiotic timing, after adjustment for potential confounding variables. Missing data other than timing were recollected from patients' charts or archived laboratory reports. Criteria for inclusion of variables in the logistics regression models were based on findings from previous studies, current clinical practice and evidence of an association ($p<0,1$) in the bivariate analysis. The appropriateness of the fitted model and its predictive utility were confirmed. Summary measures of goodness of fit were evaluated using the Hosmer-Lemeshow test. Interactions were assessed running correlation matrix and/or logit. Two- tailed p values less than 0,05 were considered statistically significant. Data were analyzed using the 'SPSS' (SPSS Inc.), and 'SAS' software.

RESULTS

Demographic, clinical and laboratory characteristics of patients are presented in table 1. The overall mortality was 22,7% (65/286).

The triad of fever, neck stiffness and change in mental status was recorded in 73,7% of patients (211/286). Only 123 (58,2%) of these patients received appropriate antibiotic treatment within 24 hours from the onset of consciousness disturbance while in 88 patients (41,7%) adequate antibiotic was applied after more than 24 hours. Favorable outcome in the former group was 60,1% (74/123) versus 17% (15/88) in the latter. 35,5% of these patients (75/211) had sought medical attention prior to admission to hospital and in 49,3% (37/75) cases inappropriate antibiotic was prescribed.

The outcome groups differed in disease severity assessed by the presence of specific organ system dysfunction or failure. The incidence of hypotension and respiratory failure which required mechanical ventilation was significantly higher in the unfavorable as opposed to the favorable group (24,8% vs. 3,1% and 76,8% vs. 13%). Some laboratory indicators of a more severe disease such as renal and liver lesion, and lower number of thrombocytes were also more often present in the unfavorable group (table 1). However, not in one patient could liver lesion be considered as liver failure. Only a mild increase of transaminases was observed.

The etiology of meningitis was confirmed in 220 (76,9%) patients. The most common pathogen was *Streptococcus pneumoniae*, followed by *Neisseria meningitidis*, *Listeria monocytogenes* and *Haemophilus influenzae*. All other Gram negative bacteria were recorded in 29 patients (10,1%). Pneumococcal disease was more common in the unfavorable group (47,2% vs. 33,5%) (table 1). Important difference was also noted for 'other Gram negative' bacteria (known as high case-fatality rate associated etiology) which were more common in the unfavorable group.

The most prominent difference was noted in antibiotic timing related to the onset of disease and the onset of consciousness disturbance which were more delayed in the unfavorable group (table 1). Appropriate treatment was started immediately (in the first hour from admission) in 263 patients (91,9%). In 23 patients the choice of antibiotic was inappropriate. We recorded a mean of 1,21 days from hospitalization to the start of appropriate therapy (table 1).

To identify possible risk factors (independent variables) of poor outcome besides antibiotic timing, a bivariate analysis was performed between the patients with poor outcome and those with favorable outcome (table 1). A bivariate analysis identified a number of factors which might increase the risks of unfavorable outcome in patients with bacterial meningitis. Among baseline parameters, advanced age and premorbid states were significantly associated with poor outcome. Other factors were those associated with clinical presentation of meningitis (disturbed consciousness, seizures, neurological deficits), and those associated with the severity of sepsis such as organ dysfunction/failures and shock. Pneumococcal disease was identified as a risk factor as well as 'other Gram negative' etiology (table 1).

These variables were included in the logistic regression analysis. Platelets count and positive CSF culture were not included in the analysis although p-value was <0.1 because we considered these differences clinically insignificant. We also excluded the use of steroids because of inconsistencies throughout the observation period particularly regarding their timing in relation to the start of antimicrobial treatment. Therefore, besides antibiotic timing according to the onset of disease, the following variables were included in the logistic regression analysis: age, presence of co-existing chronic diseases, Glasgow Coma Score, seizures, presence of focal neurological deficit, hypotension, CSF/blood glucose ratio, presence of renal lesion, liver dysfunction, and pneumococcal etiology.

The results of the multivariate analysis and independent variables included in the model are presented in table 3. Multicollinearity was not found for any combination of variables.

Likelihood ratio test showed that our model significantly better accounts for outcome than would be expected by chance (- Log likelihood difference 84,836, degrees of freedom 11, p<0,001). Model was well-fitting (chi-square 222.264, p=0.98). The model explained 82.9 % of outcomes. Delay in the appropriate treatment was significantly associated with unfavorable outcome (OR=2,8; 95%CI 1,13-7; p=0,026) (table 3). Advanced age, focal neurological deficit and disturbed consciousness expressed as lower Glasgow Coma Score were other variables associated with poor outcome. Other factors such as seizures, the presence of chronic diseases, glucose in CSF/blood ratio, renal lesion, hypotension, liver lesion and pneumococcal etiology were not independently associated with poor outcome.

The analysis of factors associated with poor outcome was repeated in a subgroup of patients with confirmed etiology and impaired consciousness. A bivariate analysis of demographic and clinical characteristics in this subgroup showed similar results as in the whole group except that the presence of focal neurological deficit and etiology were not significantly associated with unfavorable outcome (table 2). The following variables were included in the logistic regression analysis of this subgroup: age, presence of co-existing chronic diseases, Glasgow Coma Score, seizures, hypotension and CSF/blood glucose ratio and the start of appropriate therapy related to the onset of consciousness disturbance. The results of the multivariate analysis of this subgroup are shown in table 4. Likelihood ratio test showed that our model significantly better accounts for outcome than would be expected by chance (- Log likelihood difference 48.45, degrees of freedom 6, p<0.001). Model was well-fitting (chi-square 141.9 , p=0.903). The model explained 81.2 of outcomes. A delay in appropriate treatment related to the onset of consciousness disturbance was the most important variable associated with unfavorable outcome (OR=11,19; 95%CI 4,37-32,57;

p<0,001) (table 4). Advanced age, seizures and disturbed consciousness expressed as lower Glasgow Coma Score were other important variables associated with poor outcome. The presence of chronic diseases, hypotension and low glucose CSF/blood ratio were not independently associated with poor outcome.

DISCUSSION

Our retrospective, single-center study evaluated characteristics of bacterial meningitis in the fifteen-year period. We found that advanced age, disturbed consciousness, seizures and neurological deficits as well as the presence of multiorgan dysfunction and shock are independently associated with unfavorable outcome. We also found that antimicrobial treatment is also associated with clinical outcome in adult patients with community-acquired bacterial meningitis particularly when its start is related to the onset of consciousness disturbance. Other factors reported in previous studies (6-9,13,18) like comorbidity, hypotension and focal neurological deficits were not independently associated with poor outcome in our cohort of patients. The etiology of meningitis did not show a significant impact on patients' outcome.

A relatively high proportion of mechanically ventilated patients (40,9%) in our study is a consequence of disease severity. In these patients the median value of GCS was 7, and the mortality rate 55,5% (65/117).

The importance of door-to-antibiotic time was assessed in recent studies but these studies did not evaluate the duration of illness and meningitis before admission to hospital (19,20). We tried to overcome this by relating the time of appropriate therapy for meningitis to the onset of the first symptoms which might be associated with meningitis (e.g. fever, headache, vomiting, malaise etc.) and to the time of the onset of consciousness disturbance. We recognize that the definitions we used for the timing of appropriate antibiotic therapy are not

completely precise and that using hours, instead of days, would have been much more informative. Unfortunately, this is a retrospective study and precise data could not be obtained from the records of many patients. Despite this limitation, our study has showed that timing, even if represented as a dichotomous variable as we did, has an impact on disease outcome.

We recognize several other limitations of our study. The first is its retrospective nature. However, good clinical practice in our institution enabled us to collect all relevant data and include a representative number of patients satisfying acceptable power of the study. The second is that the observational period was long, and in this period a number of changes occurred, particularly in treating patients in critical care setting. Third, we were not able to assess the influence of dexamethasone treatment because of inconsistencies in its use until few years ago, when we established the necessity of its use and timing in our hospital`s treatment guidelines for adult patients with bacterial meningitis.

Despite limitations of our study, we believe that early, appropriate antibiotic treatment increases chances of favorable outcome in patients with bacterial meningitis. Only twenty percent of our patients received appropriate treatment during the first twenty-four hours of the disease. It is hard to influence the time between disease onset and the first medical contact. However, urgent diagnostic and treatment procedure in every suspicious case of bacterial meningitis during the first medical contact is of utter importance. The use of antibiotics without established diagnosis leads to a delay in adequate treatment of severe infections. We did not identify specific factors associated with tardy treatment. Other studies found that unnecessary diagnostic procedures could also result in late diagnosis and treatment of patients with bacterial meningitis (5,21,22).

In conclusion, our study emphasizes the importance of early and adequate antibiotic treatment in bacterial meningitis. Although time intervals that we used might need more strict definitions, our results showed their association with disease outcome.

The results of our study should increase alertness of physicians to diagnose and promptly treat bacterial meningitis immediately after the first contact with the patient.

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TABLE 1 Baseline demographic data and characteristics of bacterial meningitis in 286 patients

	all patients n=286	favorable group (GOS = 5) n=161	unfavorable group (GOS ≤ 4) n=125	p
age (years)				
mean±SD	47,4±18,5	40,5±17,3	56,3±16,1	<0,001
median (interquartiles)	49 (33-62)	39 (25-52)	58 (45-70)	
sex male	179 (62,58%)	103 (63,9%)	76 (60,8%)	0,66
female	107 (37,41%)	58 (36,1%)	49 (39,2%)	
co-existing diseases	117 (40,9%)	43 (26,7%)	74 (59,2%)	<0,001
prior antibiotic treatment	107 (37,4%)	61 (37,8%)	46 (36,8%)	0,94
GCS				
mean±SD	12,85±3,68	12,7±2,9	8,3±3,0	<0,001
median (interquartiles)	11(8-15)	14 (11-15)	8 (7-10)	
seizures	48 (16,7%)	12 (7,4%)	36 (28,8%)	<0,001
focal neurological deficit	28 (9,7%)	6 (3,7%)	22 (17,6%)	<0,001
triad of fever, neck stiffness and change in mental status	211 (73,7%)	90 (55,9%)	121 (96,8%)	< 0,001
adjuvant dexamethasone therapy	106 (37%)	52 (32,2%)	54 (43,2%)	0,07
hypotension	36 (12,5%)	5 (3,1%)	31 (24,8%)	<0,001
respiratory failure requiring mechanical ventilation	117 (40,9%)	21 (13%)	96 (76,8%)	<0,001
AT* - onset of disease (days)				
mean±SD	3,14±2,17	2,9±2,1	3,4±2,1	0,018
median (interquartiles)	3 (2-4)	2 (1-4)	3 (2-4)	
AT*- onset of consciousness disturbance (days)				
mean±SD	1,53±1,22	1,13±0,44	2,06±1,63	<0,001
median (interquartiles)	1 (1-2)	1 (1-1)	2 (1-2)	
AT* – time of admission to hospital (days)				
mean±SD	1,21±0,9	1,11±0,5	1,33±1,23	0,411
median (interquartiles)	1 (1-1)	1 (1-1)	1 (1-1)	
Etiology:				
S. pneumoniae	113 (39,5%)	54 (33,5%)	59 (47,2%)	0,02
Neisseria meningitidis	24 (8,3%)	19 (11,8%)	5 (4%)	0,031
Listeria monocytogenes	19 (6,6%)	12 (7,4%)	7 (5,6%)	0,70
H.influenzae	16 (5,5%)	11 (6,8%)	5 (4%)	0,43
other Gram-negative bacteria	29 (10,1%)	9 (5,5%)	20 (16%)	0,007
positive blood culture	96 (33,5%)	50 (31%)	47 (37,6%)	0,30
positive CSF culture	197 (68,8%)	104 (64,5%)	93 (74,4%)	0,09
positive Gram stain of a CSF sample	156 (54,5%)	81 (50,3%)	75 (60%)	0,13
pleocytosis (cells/3 mm^3)				
mean±SD	22007±32166	18394±19860	26660±42782	0,65
median (interquartiles)	12000 (253-26680)	13056 (3840-24320)	11264 (4800-30720)	
CSF/blood glucose ratio				
mean±SD	0,235±0,221	0,30±0,23	0,16±0,19	<0,001
median (interquartiles)	0,189 (0,022-0,385)	0,28 (0,089-0,45)	0,07 (0,01-0,27)	
renal dysfunction	43 (15%)	15 (9,3%)	28 (22,4%)	0,003
liver dysfunction	103 (36%)	38 (23,6%)	65 (52%)	<0,001
platelets count (× 109/L)				
mean±SD	194,2±96,8	199,28±81,74	187,84±113,33	0,07
median (interquartiles)	187,5 (136-235)	192 (153-235)	174 (109-234)	

* antibiotic timing according to the –

TABLE 2 Bivariate analysis of demographic data and characteristics in 176 patients with altered mental status and culture positive bacterial meningitis

	all patients n=176	favorable group (GOS = 5) n=73	unfavorable group (GOS ≤ 4) n=103	p
age (years)				
mean±SD	51,8±17,9	43,7±17,5	57,5±15,8	<0,001
median (interquartiles)	54 (39,5-65,5)	47 (29-56)	59 (47-70)	
co-existing diseases	90 (51,1%)	25 (34,2%)	65 (63,1%)	<0,001
prior antibiotic treatment	57 (32,3%)	19 (26%)	38 (36,8%)	0,175
GCS				
mean±SD	9,06±3,0	10,6±2,9	7,9±2,5	<0,001
median (interquartiles)	9 (7-11)	11 (9-13)	8 (6-10)	
seizures	39 (22,1%)	7 (9,5%)	32 (31%)	0,0013
focal neurological deficit	22 (12,5%)	5 (6,8%)	17 (16,5%)	0,093
adjuvant dexamethasone therapy	76 (43,1%)	31 (42,4%)	45 (43,6%)	0,99
hypotension	32 (18,1%)	4 (5,4%)	28 (27,1%)	<0,001
respiratory failure requiring mechanical ventilation	105 (59,6%)	19 (26%)	86 (83,4)	<0,001
AT* - onset of disease (days)				
mean±SD	3,0±2,0	2,5±1,67	3,41±2,21	0,002
median (interquartiles)	3 (2-4)	2 (1-3)	3 (2-4)	
AT*- onset of consciousness disturbance (days)				
mean±SD	1,73±1,36	1,21±0,55	2,09±1,63	<0,001
median (interquartiles)	1 (1-2)	1 (1-1)	2 (1-2)	
AT* – time of admission to hospital (days)				
mean±SD	1,27±1,0	1,09±0,41	1,4±1,34	0,351
median (interquartiles)	1 (1-1)	1 (1-1)	1 (1-1)	
Etiology:				
S. pneumoniae	100 (56,8%)	44 (60,2%)	56 (54,3%)	0,532
Neisseria meningitidis	13 (7,3%)	8 (10,9%)	5 (4,8%)	0,217
Listeria monocytogenes	14 (7,9%)	7 (9,5%)	7 (6,7%)	0,695
H.influenzae	12 (6,8%)	7 (9,5%)	5 (4,8%)	0,355
other Gram-negative bacteria	18 (10,2%)	5 (6,8%)	13 (12,6%)	0,320
positive blood culture	82 (46,5%)	37 (50,6%)	45 (43,6%)	0,445
positive CSF culture	162 (92%)	71 (97,2%)	91 (88,3%)	0,061
positive Gram stain of a CSF sample	129 (73,2%)	56 (76,7%)	73 (70,8%)	0,49
pleocytosis (cells/3 mm^3)				
mean±SD	27044±37986	24783±24629	28647±45179	0,383
median (interquartiles)	15360 (5120-33280)	16640 (8192-33280)	12800 (4800-33280)	
CSF/blood glucose ratio				
mean±SD	0,162±0,197	0,205±0,211	0,132±0,181	0,018
median (interquartiles)	0,07 (0,009-0,274)	0,159 (0,018-0,352)	0,048 (0,008-0,213)	
renal dysfunction	33 (18,7%)	9 (12,3%)	24 (23,3%)	0,1
liver dysfunction	79 (44,8%)	22 (30,1%)	57 (55,3%)	0,0016
platelets count (× 109/L)				
mean±SD	183±101	181±68	185±120	0,516
median (interquartiles)	171 (123-226)	184 (144-213)	162 (97-234)	

* antibiotic timing according to the –

TABLE 3 Logistic regression analysis of independent risk factors associated with unfavorable outcome in 286 patients with bacterial meningitis

Variable	OR	95% confidence interval	p
antibiotic timing *	2,8	1.13 – 7	0,026
age (increase per year)	1,04	1,01 - 1,06	<0,001
GCS (decrease per one point)	1,47	1,29 – 1,7	<0,001
focal neurological deficits	3.80	1.15 – 12,58	0,029
presence of chronic diseases	2.32	0.96– 3.98	0,063
seizures (yes)	2.33	0.87 – 6.24	0,09
CSF/blood glucose ratio ≤ 0.2	1.79	0,85 – 3.75	0.124
renal dysfunction	1.88	0.73 – 4.76	0.188
hypotension	3.21	0.68 – 15.08	0.140
liver dysfunction	1.77	0.87 – 3.60	0.115
pneumococcal disease	1.38	0.61 – 3.15	0.437

* start of appropriate antibiotic treatment > 24 hours after the first symptoms associated with meningitis

TABLE 4 Logistic regression analysis of independent risk factors associated with unfavorable outcome in 176 patients with altered mental status and culture positive bacterial meningitis

Variable	OR	95% confidence interval	p
antibiotic timing *	11.19	4.37 – 32.57	<0.001
age (increase per one year)	1.05	1.03 – 1.09	<0.001
GCS (decrease per one point)	1.45	1.21 – 1.74	<0.001
seizures (yes)	3.65	1.08 – 12.27	0.037
presence of chronic diseases	1.68	0.68 – 4.15	0.258
hypotension	1.57	0.28 – 8.72	0.607
CSF/blood glucose ratio ≤ 0.2	1.62	0.66 – 3.99	0.293

***** start of appropriate antibiotics >24 hours after the impairment of consciousness