UDK 616.831.9-002(497.11)"2009/2019"
COBISS.SR-ID 26266121

AKUTNI BAKTERIJSKI MENINGITISI U ZLATIBORSKOM OKRUGU

Sladana Pavić (1), Milica Jovanović (2), Miloš Božović (3), Aleksandra Pavić (4)

(1) ODELJENJE ZA INFektivNE I TROPSKE BOLESTI OPŠTE BOLNICE UŽICE, UŽICE, SRBIJA; (2) KLINIKA ZA INFektivNE I TROPSKE BOLESTI, BEOGRAD, SRBIJA; (3) ODELJENJE ZA OTORINOLARINGOLOGIJU I MAKSILOFACIJALNU HIRURGIJU OPŠTE BOLNICE UŽICE, SRBIJA; (4) MEDICINSKI FAKULTET UNIVERZITETA U BEOGRADU, BEOGRAD, SRBIJA

SAŽETAK: **Uvod:** Akutni bakterijski meningitis je prisutan u celom svetu sa letalitetom i do 50%. Najčešći uzročnici su *Streptococcus pneumoniae* i *Neisseria meningitidis*. Cilj istraživanja je analiza akutnog bakterijskog meningitisa u Zlatiborskom okrugu. **Materijal i metode:** Retrogradno je ispitivano 148 bolesnika lečenih u Opštoj bolnici Užice u desetogodišnjem periodu. Analizirani su demografski podaci, faktori rizika, hematološki i biohemijski podaci iz krvi i cerebrospinalne tečnosti ili likvora (CST) i nalaz kompjuterizovane tomografije endokranijuma. Svim bolesnicima je urađena lumbalna punkcija. Etiološka dijagnoza postavljena je identifikacijom uzročnika iz kulture cerebrospinalnog likvora (CST) ili krvi u 140 (94,6%) bolesnika a bez mikrobiološke potvrde ostalo je 8 (5,4%) bolesnika. Praćen je klinički tok, a prognoza povoljnog ishoda određena prema skor u Glasgow coma skale. **Rezultati:** Od ukupnog broja bolesnika sa akutnim bakterijskim meningitisom, 92 su bili muškarci, 56 žene, prosečne starosti 55,8 +/- 13,1 godina. Polovina ispitanika je imala komorbiditete. Kod 42% je moguće žarište infekcije bio sinuzitis. Najčešći simptomi su bili glavobolja (100%), febrilnost (97,2%) i ukočenost vrata (95,9%). Analiza cerebrospinalne tečnosti (CST) je pokazala kod 65% bolesnika manje od 100 polimorfonuklearnih leukocita/mm³ i kod 95,3% povišene vrednosti proteina u likvoru. Leukocitozu u krvi je imalo 94,6% bolesnika, a povišen C - reaktivni protein 86,5%. Najčešće izolovana bakterija bio je *Streptococcus pneumoniae* (40,5%). 74,3% bolesnika imalo je povoljan ishod bolesti. Trećina bolesnika je ispoljila epileptične napade. Kod 16,2% bolesnika bolest se završila letalno. Faktori rizika za nepovoljan ishod bili su prisustvo komorbiditeta, *Streptococcus pneumoniae* kao uzročnik bolesti, pojava epileptičkih napada, uzrast preko 50 godina i muški pol. **Zaključak:** Najčešći uzročnik akutnog bakterijskog meningitisa kod adultne populacije Zlatiborskog okruga je *Streptococcus pneumoniae* koji je, ujedno, i najčešći uzročnik nepovoljnog ishoda bolesti. Najčešće obolevaju muškarci stariji od 50 godina sa komorbiditetima koji su i rizična grupa za nepovoljan ishod bolesti.

KLjučne reči: akutni meningitis- bakterijski; Pneumokokni meningitis; akutni meningitis- faktori rizika; akutni meningitis- klinički tok; akutni meningitis- ishod bolesti

Akutni bakterijski meningitis (ABM) je infektivno oboljenje koje ima značajan morbiditet i mortalitet u celom svetu. Smrtnost kod nelečenih pacijenata dostiže 50%, a kod lečenih 8-15%. Nakon preležane bolesti, 10-20% pacijenata ima trajne neurološke i mentalne poremećaje [1]. Etiološki agensi zavise od starosnog uzrasta i geografskog područja. Kod odraslih su najčešći uzročnici *Streptococcus pneumoniae* i *Neisseria meningitidis* [2]. *Hemophilus influenzae* se sreće kao uzročnik bakterijskih meningitisa u svim uzrastima, iako je, pre primene obavezne vakcine, bio češći u populaciji dece do 5 godina [3]. Etiološka dijagnoza podrazumeva izolaciju uzročnika iz CST, ali je moguće meningizam uz prisustvo

bakterija u krvi [4]. Predisponirajući faktori za nastanak bakterijskog meningitisa podrazumevaju traumu glave, sinuzitis, otitis, faringitis, pneumoniju, ali i druga imunodeficientna stanja kao što su alkoholizam, splenektomija, neurološka i hematološka oboljenja.

CILJ

Cilj ovog ispitivanja je bio analiza epidemioloških karakteristika, etiologije, faktora rizika, kliničkog toka i prognoze akutnog bakterijskog meningitisa u populaciji odraslih osoba u Zlatiborskom okrugu.

ACUTE BACTERIAL MENINGITIS IN THE ZLATIBOR DISTRICT

Sladana Pavić (1), Milica Jovanović (2), Miloš Božović (3), Aleksandra Pavić (4)

(1) DEPARTMENT FOR INFECTIOUS AND TROPICAL DISEASES, GENERAL HOSPITAL UZICE, SERBIA; (2) CLINIC FOR INFECTIOUS AND TROPICAL DISEASES, BELGRADE, SERBIA; (3) DEPARTMENT FOR OTORHINOLARYNGOLOGY AND MAXILLOFACIAL SURGERY, GENERAL HOSPITAL UZICE, SERBIA; (4) SCHOOL OF MEDICINE UNIVERSITY OF BELGRADE, BELGRADE, SERBIA

SUMMARY: Introduction: Acute bacterial meningitis is present worldwide, with a lethality rate up to 50%. The most common causes are *Streptococcus pneumoniae* and *Neisseria meningitidis*. The aim of the research is to analyze acute bacterial meningitis in the Zlatibor district. **Material and methods:** Patients treated at the General Hospital in Uzice were examined retrogradely. Demographic data, risk factors, hematological and biochemical data from blood and cerebrospinal fluid and the findings of computed tomography scan of the endocranium were analyzed. All patients underwent lumbar puncture. The etiological diagnosis was made by identifying the pathogens from cerebrospinal fluid or blood culture. The clinical course was monitored, and the prognosis was determined according to the Glasgow coma scale. **Results:** We examined 148 patients with acute bacterial meningitis (92 men, 56 women), mean age 55.8 +/- 13.1. Half of the patients had comorbidities. In 42%, the possible focus of infection was sinusitis. Main symptoms were headache (100%), fever (97.2%), neck stiffness (95.9%). CSF analysis showed less than 100 polymorphonuclear leukocytes/mm³ in 65% of patients, and CSF protein elevation in 95.3%. 94.6% of patients had leukocytosis in the blood, and 86.5% had elevated C-reactive protein. The most commonly isolated bacterium was *Streptococcus pneumoniae* (40.5%). 74.3% of patients had a favorable disease outcome. One third of the patients showed epileptic seizures. In 16.2% of patients, the disease ended lethally. Risk factors for lethal outcome were the presence of comorbidities, *Streptococcus pneumoniae* as the pathogen, the occurrence of epileptic seizures, age over 50 years and male gender. **Conclusion:** The most common cause of acute bacterial meningitis in adult population of the Zlatibor district is *Streptococcus pneumoniae*, which is also the most common cause of adverse disease outcomes. Majority of patients are men over the age of 50 with comorbidities, which are also a risk group for an unfavorable disease outcome.

Key words: Acute Meningitis - bacterial; Pneumococcal Meningitis; Acute Meningitis- clinical course; Acute Meningitis- risk factors; Acute Meningitis-disease outcome;

INTRODUCTION

Acute bacterial meningitis (ABM) is an infectious disease with significant morbidity and mortality worldwide. Mortality in untreated patients is up to 50%, in treated 8-15%. Having gone through the disease, 10-20% of patients remain with permanent neurological and mental disorders. [1]. Etiological agents depend on age and geographical area. *Streptococcus pneumoniae* and *Neisseria meningitidis* are the most common causes of ABM in adults [2]. *Hemophilus influenzae* is the cause of ABM at all ages, more common in the population of children up to 5 years of age before the mandatory vaccine [3]. The etiological diagnosis requires isolation of the causative agent from the cerebrospinal fluid (CSF), but meningism is

possible with the presence of bacteria in the blood [4]. Predisposing factors for the development of ABM include head trauma, sinusitis, otitis, pharyngitis, pneumonia, but also other immunodeficient conditions such as alcoholism, splenectomy, neurological and hematological diseases.

THE AIM of this study was to analyze the epidemiological characteristics, etiology, risk factors, clinical course and prognosis of acute bacterial meningitis in the adult population in the Zlatibor district.

MATERIAL AND METHODS

The research included patients treated at the Department of Infectious Diseases and the Intensive Care Unit of the General Hospital Uzice, in the period from 1st. January 2009 to 31st

MATERIJAL I METODE

Istraživanje je obuhvatilo 148 bolesnika lečenih na Odeljenju za infektivne bolesti i Jedinici za intenzivnu negu Opšte bolnice Užice, u periodu od 1. 1. 2009. do 31. 12. 2019. godine. Retrospektivno su prikupljeni demografski podaci, faktori rizika, hematološki i biohemijski podaci iz krvi i CST, citološki nalaz CST-i. Analiziran je klinički tok i ishod bolesti.

Hematološke i biohemijske analize iz krvi i CST-i rađene su standardnim metodama koji se primenjuju u Republici Srbiji. Etiološka dijagnoza postavljena je identifikacijom uzročnika iz kulture CST-i ili krvi, kada je kultura CST-i bila negativna ili nedostupna. Uzorci CST-i su kultivisani na pločicama sa agarima koji sadrže 5% ovčje krvi i na čokoladnom agaru, uz inkubaciju u ugljendioksidu 24-48h na 37°C. Izolati *Streptococcus pneumoniae* i *Neisseriae meningitidis* preliminarno su identifikovani na osnovu tipičnih izgleda kolonija, bojenja po Gramu i optohinskog testa za *Streptococcus pneumoniae*. Za konačnu identifikaciju i testiranje antibiotske osetljivosti korišćen je Vitek sistem (BioMérieux, Marcy l'Etoile, France). Ispitivanje minimalne inhibitorne koncentracije vršeno je E testom, prema CLSI smernicama [5]. Svim pacijentima je urađen oftalmološki pregled očnog dna i/ili kompjuterizovana tomografija (CT) endokranijuma. Iz istraživanja su isključeni pacijenti sa tuberkuloznim meningitisom. Ishod bolesti ocenjen je na osnovu Glasgow koma skale uz sledeće vrednosti: skor 1 - smrtni ishod; skor 2 - nesposobnost bolesnika za interakciju sa okolinom; skor 3 - nesposobnost samostalnog života pacijenta, ali postoji interakcija sa okolinom; skor 4 - sposobnost samostalnog života uz poslovnu nesposobnost;

skor 5 - radna sposobnost. Povoljan ishod bolesti je definisan skorom 5, dok su skorovi od 1 do 4 označeni kao nepovoljan ishod [6].

Za statističku analizu korišćen je Statistički paket za društvene nauke SPSS (verzija 16.0). Značajnu razliku predstavljao je $P < 0.05$.

REZULTATI

Od ukupnog broja ispitanika sa akutnim bakterijskim meningitisom (148), muškaraca je bilo 92, žena 56, uzrasta od 22 do 84 godine, prosečno 55,8+/-13,1.

Značajan broj ispitanika je imao prethodne udružene bolesti. Trećina je imala šećernu bolest i kardiološka oboljenja, dok je 22,3% prekomerno konzumiralo alkohol. Kod 88,5% ispitanika moglo se pretpostaviti poreklo infekcije. Značajno najčešća bila je prethodna upala sinusa, kod 41,9%. Kod 19,6% bolesnika akutnom bakterijskom meningitisu je prethodila upala uha, a kod 12,8% upala ždrela. Svi bolesnici su pri prijemu osećali glavobolju, kod 97,2% je bila povišena telesna temperatura, 95,9% ukočenost vrata pri antefleksiji glave. Povraćanje i fotofobija su bili prisutni kod 76,3%, odnosno 75,6%. Nije bilo statistički značajne razlike između prisustva navedenih simptoma.

Svim bolesnicima je urađen oftalmološki pregled očnog dna. Kompjuterizovana tomografija endokranijuma je urađena kod 82,4%. Signifikantno najčešći je bio patološki nalaz u sinusnim šuplinama, kod 41,9%.

Epidemiološke karakteristike, komorbiditeti, moguća žarišta infekcije, simptomi i nalaz CT endokranijuma prikazani su u tabeli 1.

Tabela 1. Epidemiološki parametri, komorbiditeti, žarište infekcije, simptomi i CT nalaz kod bolesnika sa ABM

Karakteristike		ABM No (%)	*p
Uzrast	21-30	9 (6.1)	0.00
	31-40	13 (8.8)	
	41-50	27 (18.2)	
	51-60	49 (33.1)	
	61-70	32 (21.6)	
	71-80	14 (9.5)	
	> 80	4	
Pol	Muškarci	92 (62.2)	0.003
	Žene	56 (37.8)	
	Diabetes mellitus	48 (32.4)	0.00
	HTA/CMP	50 (33.8)	
	Astma/HOBP	22 (14.9)	

December 2019. Demographic data, risk factors, hematological and biochemical data from blood and CSF, cytological findings of CSF were collected retrospectively. The clinical course and outcome of the disease were analyzed, too.

Hematological and biochemical analyses from blood and CSF were performed by standard methods used in the Republic of Serbia. The etiological diagnosis was made by identifying the causative agent from CSF culture or blood, when CSF culture was negative or unavailable. Samples of CSF were cultured on blood agar plates containing 5% sheep blood and on chocolate agar, incubated in carbon dioxide for 24 - 48 h at 37° C. Isolates of *Streptococcus pneumoniae* and *Neisseriae meningitidis* were preliminarily identified based on typical colonial prospects, Gram staining and optochin test for *Streptococcus pneumoniae*. The Vitek system (bioMérieux, Marcy l'Etoile, France) was used for the final identification and testing of antibiotic susceptibility. The minimum inhibitory concentration test was performed by the E test, according to CLSI guidelines [5].

All patients underwent ophthalmic examination of the fundus and/or computed tomography (CT) scan of the endocranium.

Patients with tuberculous meningitis were excluded from the study.

The outcome of the disease was assessed on the basis of the Glasgow Coma Scale with the following values:

score 1 - death; score 2 - inability of patients to interact with the environment; score 3 - inability of the patient to live independently, but there is an interaction with the environment; score 4 - ability to live independently with incapacity for

work; score 5 - working ability. The favorable outcome of the disease was defined by a score of 5, while scores 1 to 4 were marked as an unfavorable outcome [6].

The Statistical Package for Social Sciences SPSS (version 16.0) was used for statistical analysis. A significant difference was represented by $P < 0.05$.

RESULTS

A total of 148 patients with ABM was examined, 92 men and 56 women, aged 22 to 84 years of age, averaged 55.8 ± 13.1 .

A significant number of patients had comorbidities. A third of patients had diabetes and heart disease, 22.3% consumed alcohol excessively. The origin of the infection could be assumed in 88.5% of the patients. Sinusitis was significantly the most common at 41.9%. In 19.6% of patients, ABM was preceded by ear inflammation, in 12.8% by pharyngitis. All patients experienced headache on admission, 97.2% had fever, and 95.9% had neck stiffness during head anteflexion. Vomiting and photophobia were present in 76.3% and 75.6%, respectively. There was no statistically significant difference between the presence of these symptoms.

All patients underwent ophthalmologic examination of the fundus. CT scan of the endocranium was performed in 82.4%. Pathological finding in the sinus cavities was significantly the most common in 41.9%.

Epidemiological characteristics, comorbidities, possible focus of infection, symptoms and findings of CT scan of the endocranium are shown in Table 1.

Table 1. Epidemiological parameters, comorbidities, focus of infection, symptoms and CT scan finding in patients with ABM

Characteristics		ABM No (%)	*P
Age	21-30	9 (6.1)	0.00
	31-40	13 (8.8)	
	41-50	27 (18.2)	
	51-60	49 (33.1)	
	61-70	32 (21.6)	
	71-80	14 (9.5)	
	> 80	4	
Gender	Male	92 (62.2)	0.003
	Female	56 (37.8)	
Comorbidities	Diabetes mellitus	48 (32.4)	0.00
	HTA/CMP	50 (33.8)	
	Asthma/COPD	22 (14.9)	
	Alcoholism	33 (22.3)	

Komorbiditeti	Alkoholizam	33 (22.3)	0.00
	Neurološka oboljenja	27 (18.2)	
	Psihijatrijska oboljenja	9 (6.1)	
	Ukupno	75 (50.7)	
Verovatna žarišta infekcije	Trauma glave	7 (4.7)	0.00
	Otitis	29 (19.6)	
	Sinusitis	62 (41.9)	
	Dentalne infekcije	7 (4.7)	
	Pharyngitis	19 (12.8)	
	Pneumonia	9 (6.1)	
	Nepoznato	15 (10.1)	
Simptomi pri prijemu	Glavobolja	148 (100)	0.06
	Povraćanje	113 (76.3)	
	Fotofobija	112 (75.6)	
	Ukočenost vrata	142 (95.9)	
	Febrilnost > 38o	144 (97.2)	
CT endokranijuma	Cerebralni edem	38 (21.6)	0.00
	Promene u sinusima	62 (41.9)	
	Mastoiditis	6 (4.1)	
	Hidrocephalus	2	
	Skoriji infarkt mozga	14 (9.5)	

*P - statisticka značajnost za uzorke ≥ 5

Svim bolesnicima je urađena lumbalna punkcija. Broj polimorfonuklearnih leukocita bio je signifikatno najčešće do $100/\text{mm}^3$. Kod značajne većine bolesnika (95,3%) proteini u likvoru su bili povišeni, dok je indeks glukoza u likvoru/glukoza u krvi bio snižen kod 40,5% ispitanika. Vrednost proteina u likvoru bila je od 0,22 – 6,1 g/L, prosečno 2.8 ± 2.2 g/L.

Najčešći uzročnici ABM bili su *Streptococcus pneumoniae* i *Neisseria meningitidis*, kod 40,5%, odnosno 26,3%. Drugi uzročnici su bili značajno ređi.

Serumski biohemijski parametri bakterijske infekcije, leukocitoza i povišene vrednosti CRP-a imao je signifikatno značajan broj bolesnika, 94,6%, odnosno 86,5%. Broj leukocita je bio od $5,6$ do $16,2 \times 10^9/\text{L}$, prosečno $12,4 \times 10^9/\text{L}$. Interval vrednosti CRP-a iznosio je od 3,4 - 122 mg/L, prosečno $34,1 \pm 45,2$ mg/L.

Biohemijski nalazi iz krvi i likvora, citološki nalaz likvora i etiološki uzročnici akutnih bakterijskih meningitisa prikazani su u tabeli 2.

Tabela 2. Biohemijski nalazi krvi i CST-i, citološki nalaz CST-i i etiološki uzročnici ABM

Laboratorijski parametri		ABM No (%)	P
Leukociti ($\times 10^9/\text{L}$)	>10	140 (94.6)	0.00
C - reaktivni protein (mg/L)	>10	128 (86.5)	0.00
CST broj polimorfonukleara/ mm^3	< 100	96 (64.9)	0.00
	100 - 1000	40 (27)	
	> 1000	12 (8.1)	
CST proteini (g/L)	> 0.47	141 (95.3)	0.00
CST glukoza/glukoza u krvi mmol/L)	< 1/3	60 (40.5)	0.06
Izolati iz CST-i	<i>Streptococcus pneumoniae</i>	60 (40.5)	0.00
	<i>Neisseria meningitidis</i>	39 (26.3)	
	<i>Hemophilus influenzae</i>	12 (8.1)	
	<i>Staphylococcus aureus</i>	10 (6.8)	
	<i>Listeria monocytogenes</i>	5 (3.4)	
	<i>Escherichia coli</i>	5 (3.4)	
	Ukupno izolata iz CST-i	131 (88.5)	
Izolati iz hemokultura		9 (6.1)	0.00
Bez mikrobiološke potvrde		8 (5.4)	0.00

Klinički tok je kod značajne većine (74,3%) bolesnika završen povoljno. Epileptične napade je imala trećina bolesnika. Kod 24 (16,2%) bolesnika bolest se završila letalno

(tabela 3). Među bolesnicima sa letalnim ishodom, epileptične napade je imalo 19

	Neurological diseases	27 (18.2)	0.00
	Psychiatric diseases	9 (6.1)	
	Total	75 (50.7)	
Probable focus of infection	Head trauma	7 (4.7)	0.00
	Otitis	29 (19.6)	
	Sinusitis	62 (41.9)	
	Dental infections	7 (4.7)	
	Pharyngitis	19 (12.8)	
	Pneumonia	9 (6.1)	
Symptoms on admission	Headache	148 (100)	0.06
	Vomiting	113 (76.3)	
	Photophobia	112 (75.6)	
	Neck stiffness	142 (95.9)	
	Fever > 38o	144 (97.2)	
CT scan of the endocranium	Cerebral edema	38 (21.6)	0.00
	Content in the sinuses	62 (41.9)	
	Mastoiditis	6 (4.1)	
	Hydrocephalus	2	
	Recent cerebral infarction	14 (9.5)	

*P - statistical significance for samples ≥ 5

All patients underwent lumbar puncture. The number of polymorphonuclear leukocytes was significantly up to 100/mm³. In a significant majority of patients (95.3%), CSF proteins were elevated, while CSF/blood glucose index was reduced in 40.5% of subjects. The value of protein in the CSF was from 0.22 - 6.1 g / L, on average 2.8 +/- 2.2 g / L.

The most common causes of ABM were *Streptococcus pneumoniae* and *Neisseria meningitidis*, in 40.5% and 26.3%, respectively. Other pathogens were significantly rarer.

Serum biochemical parameters of bacterial infection, leukocytosis and elevated C-reactive protein (CRP) level, were observed in a significant number of patients, 94.6% and 86.5%, respectively. The leukocyte count ranged from 5.6 to 16.2x10⁹ / L, averaging 12.4x10⁹/L. The CRP value range was 3.4 - 122 mg/L, averaging 34.1 +/- 45.2 mg / L.

Biochemical findings from blood and cerebrospinal fluid, cytological findings of cerebrospinal fluid and etiological causes of acute bacterial meningitis are shown in Table 2.

Table 2. Biochemical findings of blood and CSF, cytological findings of CSF and etiological agents of ABM

Laboratory parameters		ABM No (%)	P
WBC (x10 ⁹ /L)	>10	140 (94.6)	0.00
C - reactive protein (mg/L)	>10	128 (86.5)	0.00
CSF polymorphonuclear/mm ³	< 100	96 (64.9)	0.00
	100 - 1000	40 (27)	
	> 1000	12 (8.1)	
CSF protein (g/L)	> 0.47	141 (95.3)	0.00
CSF glucose/serum glucose (mmol/L)	< 1/3	60 (40.5)	0.06
CSF isolates	<i>Streptococcus pneumoniae</i>	60 (40.5)	0.00
	<i>Neisseria meningitidis</i>	39 (26.3)	
	<i>Hemophilus influenzae</i>	12 (8.1)	
	<i>Staphylococcus aureus</i>	10 (6.8)	
	<i>Listeria monocytogenes</i>	5 (3.4)	
	<i>Escherichia coli</i>	5 (3.4)	
Blood culture isolates		9 (6.1)	

The clinical course was favorable in a significant majority (74.3%) of the patients. One third of

patients had epileptic seizures. In 24 (16.2%) patients the disease ended lethally (Table 3).

(79.2%) bolesnika, što predstavlja značajnu većinu ($p = 0.00$)

Tabela 3. Klinički tok i ishod bolesnika sa ABM

Klinički tok	ABM No (%)	*P
Fokalni neurološki ispadi	2	
EPI napadi	49 (33.1)	0.001
Kardiorespiratorni poremećaji	9 (6.1)	0.00
Izmene u mentalnom statusu	4	
Glasgow koma skala pri otpustu	1	24 (16.2)
	2	2
	3	4
	4	8 (5.4)
	5	110 (74.3)

*P - statistička značajnost za uzorke ≥ 5

Dalje su ispitivani faktori rizika za nepovoljan ishod bolesti (tabela 4)

Tabela 4. Faktori rizika za nepovoljan ishod ABM

Faktori rizika	ABM povoljan ishod N (%) 110 (74.3)	ABM nepovoljan ishod No (%) 38 (25.6)	P
Uzrast > 50 godina	64 (56.4)	35 (86.8)	0.011
Muški pol	80 (52.7)	12 (31.6)	0.020
Komorbiditeti	46 (41.8)	29 (76.3)	< 0.01
Sinuzitis	48 (43.6)	14 (36.8)	0.458
Epi napadi	29 (26.4)	20 (52.6)	0.003
Leukociti ($\times 10^9$ /L) > 10	105 (95.5)	35 (92.1)	0.803
C - reaktivni protein (mg/L) > 10	100 (90.9)	28 (73.7)	0.180
CST broj polimorfonukleara/mm ³ < 100	68 (61.8)	28 (73.7)	0.306
CST proteini (g/L) > 0.47	105 (95.5)	36 (94.7)	0.956
Streptococcus pneumoniae	36 (32.7)	24 (63.2)	0.002

Značajni faktori za nepovoljan ishod akutnog bakterijskog meningitisa bilo je prisustvo komorbiditeta, Streptococcus pneumoniae kao uzročnik bolesti, pojava epileptičkih napada, uzrast preko 50 godina i muški pol.

DISKUSIJA

Analiza uzročnika bakterijskih meningitisa posljednjih godina ukazala je na razlike u zavisnosti od širokog raspona ispitivanih starosnih grupa [7]. U odrasloj populaciji su najčešći uzročnici Streptococcus pneumoniae i Neisseria meningitis, dok su kod dece najčešći Streptococcus agalactiae, Escherichia coli, Listeria monocytogenes [8]. Naše istraživanje je obuhvatilo adultnu populaciju i učestalost pojedinih uzročnika odgovara prethodno navedenom zaključku drugih istraživača. Mikrobiološka potvrda izostala je u našem ispitivanju kod 8 (5,4%) bolesnika. Pretpostavljamo da je razlog primena antibiotske terapije pre uzimanja CST-i za

analizu. S obzirom na laboratorijske parametre koji su odgovarali bakterijskoj infekciji, ovi pacijenti su dalje lečeni po protokolu za lečenje ABM nepoznatog uzročnika i svi su imali povoljan klinički tok bolesti.

Haemophilus influenzae je patogen dečjeg uzrasta, značajno ređi nakon što je vakcina postala obavezna [8]. U našem istraživanju je bio prisutan u 8,1%, što je očekivano s obzirom da je najčešći kolonizator sluznice respiratornog trakta, a posebno čest kod osoba sa hroničnom opstruktivnom bolešću pluća [9].

Demografski podaci su pokazali da su kod nas muškarci više obolevali, što je u skladu sa nalazima Diasa i saradnika koji su dokazali da su muškarci sa akutnim bakterijskim meningitisom imali češće traume glave i prekomerno konzumiranje alkohola kao faktore rizika [10]. Glavni faktor rizika naših ispitanika bio je sindrom srčane insuficijencije (hipertenzivno i ishemijsko oštećenje miokarda). Ovo je u skladu sa činjenicom da su naši pacijenti

Table 3. Clinical course and outcome of patients with ABM

Clinical course of diseases		ABM No (%)	*P
Focal neurological changes		2	
Epileptic seizures		49 (33.1)	0.001
Cardiorespiratory changes		9 (6.1)	0.00
Changes in mental status		4	
Glasgow coma scale at discharge	1	24 (16.2)	0.00
	2	2	
	3	4	
	4	8 (5.4)	
	5	110 (74.3)	

*P - statistical significance for samples ≥ 5

Risk factors for unfavorable disease outcome were further examined (Table 4)

Table 4. Risk factors for unfavorable outcome of ABM

Risk factors	ABM favorable outcome N (%) 110 (74.3)	ABM unfavorable outcome No (%) 38 (25.6)	P
Age > 50	64 (56.4)	35 (86.8)	0.011
Male	80 (52.7)	12 (31.6)	0.020
Comorbidities	46 (41.8)	29 (76.3)	< 0.01
Sinusitis	48 (43.6)	14 (36.8)	0.458
Epileptic seizures	29 (26.4)	20 (52.6)	0.003
WBC ($\times 10^9$ /L) > 10	105 (95.5)	35 (92.1)	0.803
C - reactive protein (mg/L) >10	100 (90.9)	28 (73.7)	0.180
CSF polymorphonuclear/mm ³ <100	68 (61.8)	28 (73.7)	0.306
CSF protein (g/L) > 0.47	105 (95.5)	36 (94.7)	0.956
Streptococcus pneumoniae	36 (32.7)	24 (63.2)	0.002

Significant factors for the unfavorable outcome of acute bacterial meningitis were the presence of comorbidities, Streptococcus pneumoniae as the cause of the disease, the occurrence of epileptic seizures, age over 50 and male gender.

DISCUSSION

Analysis of the causes of ABM has indicated differences depending on a wide range of examined age groups in recent years [7]. The most common causes are Streptococcus pneumoniae and Neisseria meningitis in adult population, while in children the most common are Streptococcus agalactiae, Escherichia coli, Listeria monocytogenes [8]. Our study included adult population and the frequency of individual pathogens corresponds to the above conclusion of other researchers. Haemophilus influenzae is a childhood pathogen, significantly rarer after the vaccine became mandatory [8]. In our study, it was present in 8.1%, which is expected given that it is the most common colonizer of the respiratory tract mucosa, and especially

common in persons with chronic obstructive pulmonary disease [9].

Demographic data showed that men got sick more often, which corresponds to the finding of Diaz and colleagues who proved that men with ABM have more frequent head trauma and excessive alcohol consumption as risk factors [10]. The main risk factor of our patients was hypertension/cardiomyopathy. This can be explained by older age of the patients. Diabetes mellitus was the second most important risk factor. Diabetes leads to changes in body's immune defenses. The function of polymorphonuclear leukocytes is reduced, especially when acidosis is also present. Leukocyte adhesion, chemotaxis, and phagocytosis were also altered and antioxidant bactericidal systems were weakened [11].

Inflammation of the sinuses and ear are more common possible sources of infection in our patients, unlike other studies [12]. This result can be explained by the proven high percentage of bacterial sinusitis in the adult population [13, 14]. This finding is supported by the finding of CT scan, which most often

u velikoj većini bili starije životne dobi. Drugi po značaju faktor rizika bio je diabetes mellitus. Šećerna bolest dovodi do izmena u imunološkoj odbrani organizma. Smanjena je funkcija polimorfonuklearnih leukocita, posebno kada je prisutna i acidoza. Takođe je izmenjena leukocitna adhezija, hemotaksija i fagocitoza, a oslabljeni su i antioksidantni baktericidni sistemi [11].

Naši ispitanici su češće od ispitanika u drugim istraživanjima imali upale sinusa i uha koje su prethodile nastanku bakterijskog meningitisa, pa su smatrane verovatnim žarištima [12]. Taj rezultat se može objasniti dokazanim visokim procentom bakterijskog sinuzitisa u odrasloj populaciji [13,14]. U prilog ovom nalazu ide i nalaz kompjuterizovane tomografije koji je najčešće ukazivao na patološki proces u sinusima. Kod 10.1% naših bolesnika nismo otkrili verovatno žarište infekcije. Ovome je doprinela i činjenica da neki bolesnici zbog kliničkog stanja (visoke febrilnosti, somnolencije i sl.) nisu mogli da daju precizne podatke o početku bolesti koji bi ukazali na žarište infekcije, niti je heteroanamnestički bilo moguće dobiti takve podatke.

Pored glavobolje, ukočenost vrata i febrilnost su bili najčešći simptomi i drugih istraživanja uz prisustvo izmene mentalnog statusa [12]. Klinički tok naših bolesnika bio je praćen pojavom epileptičnih napada kod trećine. Infekcije CNS-a kao uzrok nastanka epilepsije prisutne su kod četvrtine bolesnika sa ABM [15]. Dokazano je da epileptični napadi korelišu sa nižim vrednostima šećera i višim vrednostima proteina u CST-i [16]. Faktori rizika za nastajanje kasnijih neprovociranih napada podrazumevaju fokalno pražnjenje, oštre elektroencefalografske talase i početne vrednosti glukoze u likvoru <20 mg/dl [17]. Citološki nalaz likvora sa pleocitozom uz dominaciju polinuklearnih neutrofila je standardni nalaz kod bakterijskih meningitisa, što odgovara i našim rezultatima. Povišene vrednosti proteina, prusutne kod značajne većine naših ispitanika, očekivan su nalaz kod bakterijskog meningitisa, iako se u literaturi sreću podaci da 1-10% pacijenata nema povišene vrednosti proteina u likvoru [18]. Vrednost glukoze u likvoru bila je snižena kod 40% naših ispitanika. Ovo je u skladu sa drugim podacima kod kojih se opisuje manje od 50% pacijenata sa sličnim nalazom. Rezultati upućuju

na nisku senzitivnost analize, što ovaj parametar čini nepouzdanim pri postavljanju dijagnoze bakterijskog meningitisa [19].

Serumski parametar inflamacije, C - reaktivni protein, bio je povišen kod velikog procenta naših bolesnika. Analizom ovog parametra, Brouwer i saradnici su istakli njegovu nepouzdanost kod dijagnostike ABM [20]. S obzirom na rezultat povišenog C - reaktivnog proteina kod 86.5% naših bolesnika, možemo istaći visoku senzitivnost ovog inflamatornog parametra.

Nepovoljan klinički tok kod naših pacijenata manji je od opisanog [12]. Uzročnik letalnog ishoda najčešće je *Streptococcus pneumoniae*. Najznačajni faktori rizika za letalni ishod naših bolesnika su uzrast preko 50 godina i prisustvo komorbiditeta. S obzirom na naš rezultat, bilo bi opravdano da osobe starije od 50 godina koje imaju druge udružene bolesti prime vakcinopofilaksu za *Streptococcus pneumoniae*. Naš nalaz je delimično u skladu sa nalazima drugih autora koji pominju najčešći uzrast iznad 65 godina [12]. Ispitanici nižih autora bili su većinom iste starosne grupe kao i naši, pri čemu su istraživači uočili da starije osobe na početku bolesti često imaju oskudniju simptomatologiju [21]. Mali procenat bakterijskih izolata iz CST-i autori objašnjavaju primenom antibiotske terapije pre uzimanja CST-i. Ovo može odložiti postavljanje dijagnoze i nepovoljno uticati na dalji klinički tok i ishod bolesti.

Interesantni su zaključci autora koji su ispitivali uticaj klimatskih faktora na pojavu bakterijskog meningitisa i dobili pozitivnu korelaciju sa pojavom vetra i magle, a negativnu sa osunčavanjem [22]. Može se pretpostaviti da bi bilo korisno analizirati klimatske podatke i kod naših bolesnika.

ZAKLJUČAK

Od velike važnosti za svako geografsko područje predstavlja očekivani uzročnik bolesti kod određene populacije bolesnika. Najčešći uzročnik akutnog bakterijskog meningitisa kod adultne populacije Zlatiborskog okruga je *Streptococcus pneumoniae*, kod 40,5% bolesnika, koji je ujedno i najčešći uzročnik nepovoljnog ishoda bolesti. Druga po učestalosti je *Neisseria meningitidis* (26,3%). Najčešće obolevaju muškarci u šestoj deceniji života koji pri tom imaju teže komorbiditete. Ukoliko se u kliničkom toku ove populacije ispolje epileptički napadi, prisutni su svi rizični faktori za

indicated a pathological process in the sinuses. In addition to headache, neck stiffness and fever with a change in mental status were the most common symptoms of both our study and others. [12]. The clinical course of our patients was accompanied by the occurrence of epileptic seizures in one third of patients. CNS infections as a cause of epilepsy are present in a quarter of patients with ABM [15]. Epileptic seizures have been shown to correlate with lower sugar values and higher protein values in CSF [16]. Risk factors for subsequent unprovoked seizures include focal discharge, sharp electroencephalographic waves, and initial CSF glucose <20 mg / dl [17]. The cytological finding of CSF with pleocytosis with the dominance of polynuclear neutrophils is a standard finding in ABM, which corresponds to our results. Elevated protein values present in a significant majority of our patients are expected findings for bacterial meningitis, although there are data in literature that 1-10% of patients with ABM do not have elevated CSF protein [18]. The value of glucose in CSF was reduced in 40% of our patients. This is consistent with other data describing less than 50% of patients with similar findings. The results indicate the unreliability of this parameter in the diagnosis of bacterial meningitis [19].

The serum parameter of inflammation, C - reactive protein, was elevated in a large percentage of our patients. Browver and coauthors pointed out the unreliability of CRP values in the diagnosis of ABM [20].

The unfavorable clinical course in our patients is smaller than described [12]. The most common cause of death is *Streptococcus pneumoniae*. The most significant risk factors are advanced age and the presence of comorbidities, which corresponds to the findings of other authors [12]. Our finding is partly consistent with the findings of other authors

who mention the most common age over 65 years [12]. Respondents from Nis authors were mostly of the same age group as ours, with researchers noting that older people often have more sparse symptoms at the beginning of the disease [21]. The authors explain the small percentage of bacterial isolates from CSTs by using antibiotic therapy before taking CSTs. This can delay the diagnosis and adversely affect the further clinical course and outcome of the disease. Interesting are the conclusions of the authors who examined the influence of climatic factors on the occurrence of bacterial meningitis and obtained a positive correlation with the occurrence of wind and fog, and a negative correlation with insolation [22]. It can be assumed that it would be useful to analyze climate data in our patients as well.

CONCLUSION

The expected causative agent of a disease in a patient population is of great importance for each geographical area. The most common cause of acute bacterial meningitis in the adult population of Zlatibor district is *Streptococcus pneumoniae*, in 40.5% of patients, which is also the most common cause of adverse disease outcomes. The second most common is *Neisseria meningitidis* (26.3%). ABM is most common in men in their sixth decade of life who have comorbidities. The occurrence of epileptic seizures during ABM is also a risk factor of unfavorable outcomes of disease. The source of ABM is most often in the sinuses or ear, so timely treatment of these infections is an important preventive measure. Since there is a vaccine prophylaxis for *Streptococcus pneumoniae* and *Neisseria meningitidis*, it is necessary to recommend this preventive measure to the elderly, especially those who have comorbidities.

REFERENCES

1. World Health Organization (WHO). Meningococcal meningitis: Fact sheet 2017 [updated December 2017; cited 2017 November 9]. Dostupno na: <http://www.who.int/mediacentre/factsheets/fs141/en/>.
2. Centers for Disease Control and Prevention (CDC). Bacterial Meningitis 2017 [updated January 25, 2017]. Dostupno na: <https://www.cdc.gov/meningitis/bacterial.html>.
3. World Health Organization (WHO). Haemophilus influenzae type b (Hib) Vaccination Position Paper July 2013. Releve epidemiologique hebdomadaire. 2013; 88 (Suppl 39): 413-26.
4. McGill F, Heyderman RS, Michael BD, et al. The UK joint specialist societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults. J Infect. 2016; 72: 405-38.
5. European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters, 2011 EUCAST Version 1.3. Available from: http://www.eucast.org/clinical_breakpoints/
6. Jennett B, Teasdale G. Management of head injuries. 2nd ed. Philadelphia: F.A. Davis, 1981.
7. Oordt-Speets AM, Bolijn R, van Hoorn RC, Bhavsar A, Kyaw MH. Global etiology of bacterial meningitis: A systematic review and meta-analysis. PLoS ONE

nepovoljan ishod bolesti. Žarište infekcije je najčešće u sinusima ili uhu, pa je pravovremeno lečenje ovih infekcija važna preventivna mera. S obzirom da za *Streptococcus pneumoniae* i *Neisseriu meningitidis* postoji vakcinoprofilaksa,

potrebno je preporučiti ovu preventivnu meru osobama starije životne dobi, posebno onima koji imaju komorbiditete.

LITERATURA:

1. World Health Organization (WHO). Meningococcal meningitis: Fact sheet 2017 [updated December 2017; cited 2017 November 9]. Dostupno na: <http://www.who.int/mediacentre/factsheets/fs141/en/>.
2. Centers for Disease Control and Prevention (CDC). Bacterial Meningitis 2017 [updated January 25, 2017]. Dostupno na: <https://www.cdc.gov/meningitis/bacterial.html>.
3. World Health Organization (WHO). Haemophilus influenzae type b (Hib) Vaccination Position Paper July 2013. *Releve epidemiologique hebdomadaire*. 2013; 88 (Suppl 39): 413-26.
4. McGill F, Heyderman RS, Michael BD, et al. The UK joint specialist societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults. *J Infect*. 2016; 72: 405-38.
5. European Committee on Antimicrobial Susceptibility Testing, Breakpoint tables for interpretation of MICs and zone diameters, 2011 EUCAST Version 1.3. Available from: http://www.eucast.org/clinical_breakpoints/
6. Jennett B, Teasdale G. Management of head injuries. 2nd ed. Philadelphia: F.A. Davis, 1981.
7. Oordt-Speets AM, Bolijn R, van Hoorn RC, Bhavsar A, Kyaw MH. Global etiology of bacterial meningitis: A systematic review and meta-analysis. *PLoS ONE* 2018;13(6):e0198772. Available from: <https://doi.org/10.1371/journal.pone.0198772>.
8. Brouwer MC, Tunkel AR, van de Beek D. Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. *Clinical microbiology reviews*. 2010; 23 (Suppl 3): 467-92.
9. Murphy TF, Brauer AL, Sethi S, Kilian M, Cai X, Lesse AJ. Haemophilus haemolyticus: a human respiratory tract commensal to be distinguished from Haemophilus influenzae. *J Infect Dis*. 2007; 195 (Suppl 1): 81-9.
10. Yerramilli A, Mangapati P, Prabhakar S, Sirimulla H, Shravani Vanam S, Voora Y. A study on the clinical outcomes and management of meningitis at a tertiary care centre. *Neurol India*. 2017; 65 (Suppl 5):1006-12.
11. Joshi N, Gregory M, Caputo, Michael R, Weitekamp, A.W. Karchmer. Infections in patients with diabetes mellitus. *N Eng J Med*. 1999; 341: 1906-12.
12. Beek D, Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical Features and Prognostic Factors in Adults with Bacterial Meningitis. *N Engl J Med*. 2004; 351: 1849-59.
13. Sami AS, Scadding GK, Howarth P. A UK Community-Based Survey on the Prevalence of Rhinosinusitis. *Clin Otolaryngol*. 2018;43 (Suppl 1): 76-89.
14. Bhattacharyya N, Gilani S. Prevalence of Potential Adult Chronic Rhinosinusitis Symptoms in the United States. *Otolaryngol Head Neck Surg*. 2018; 159 (Suppl 3): 522-5.
15. Preux PM, Druet-Cabanac M. Epidemiology and etiology of epilepsy in sub-Saharan Africa. *Lancet Neurol* 2005; 4: 21-31.
16. Chang CJ, Chang HW, Chang WN, Huang LT, Huang SC, Chang YC, Hung PL, Chang CS, Chuang YC, Huang CR, Tsai NW, Tsui HW, Wang KW, Lu CH. Seizures complicating infantile and childhood bacterial meningitis. *Pediatr Neurol* 2004; 31: 165-71.
17. Pomeroy SL, Holmes SJ, Dodge PR, Feigin RD. Seizures and other neurologic sequelae of bacterial meningitis in children. *N Engl J Med*. 1990; 323: 1651-7.
18. Viallon A, Botelho-Nevers E, Zeni F. Clinical decision rules for acute bacterial meningitis: current insights. *Open Access Emergency Medicine* 2016; 8: 7-16.
19. Durand ML, Calderwood SB, Weber DJ, et al. Acute bacterial meningitis in adults. A review of 493 episodes. *N Engl J Med*. 1993; 328 (Suppl 1): 21-8.
20. Brouwer MC, Thwaites GE, Tunkel AR, Van De Beek D. Dilemmas in the diagnosis of acute community-acquired bacterial meningitis. *Lancet*. 2012; 380 (9854): 1684-92.
21. Ranković A, Vrbić M, Jovanović M, Popović-Dragonjić L, Đorđević-Spašić M. Meningeal syndrome in the practice of Infectious diseases. *Acta Medica Medianae* 2017; 56(2): 32-7.
22. Janković Lj, Pantović V, Damjanov V. Korelacija između klime i bakterijskog meningitisa. *Medicus* 2006;7 (1):29-31.

- 2018;13(6):e0198772. Available from: <https://doi.org/10.1371/journal.pone.0198772>.
8. Brouwer MC, Tunkel AR, van de Beek D. Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. *Clinical microbiology reviews*. 2010; 23 (Suppl 3): 467-92.
 9. Murphy TF, Brauer AL, Sethi S, Kilian M, Cai X, Lesse AJ. *Haemophilus haemolyticus*: a human respiratory tract commensal to be distinguished from *Haemophilus influenzae*. *J Infect Dis*. 2007; 195 (Suppl 1): 81-9.
 10. Yerramilli A, Mangapati P, Prabhakar S, Sirimulla H, Shravani Vanam S, Voora Y. A study on the clinical outcomes and management of meningitis at a tertiary care centre. *Neurol India*. 2017; 65 (Suppl 5):1006-12.
 11. Joshi N, Gregory M, Caputo, Michael R, Weitekamp, A.W. Karchmer. Infections in patients with diabetes mellitus. *N Eng J Med*. 1999; 341: 1906-12.
 12. Beek D, Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical Features and Prognostic Factors in Adults with Bacterial Meningitis. *N Engl J Med*. 2004; 351: 1849-59.
 13. Sami AS, Scadding GK, Howarth P. A UK Community-Based Survey on the Prevalence of Rhinosinusitis. *Clin Otolaryngol*. 2018;43 (Suppl 1): 76-89.
 14. Bhattacharyya N, Gilani S. Prevalence of Potential Adult Chronic Rhinosinusitis Symptoms in the United States. *Otolaryngol Head Neck Surg*. 2018; 159 (Suppl 3): 522-5.
 15. Preux PM, Druet-Cabanac M. Epidemiology and etiology of epilepsy in sub-Saharan Africa. *Lancet Neurol* 2005; 4: 21-31.
 16. Chang CJ, Chang HW, Chang WN, Huang LT, Huang SC, Chang YC, Hung PL, Chang CS, Chuang YC, Huang CR, Tsai NW, Tsui HW, Wang KW, Lu CH. Seizures complicating infantile and child-hood bacterial meningitis. *Pediatr Neurol* 2004; 31: 165-71.
 17. Pomeroy SL, Holmes SJ, Dodge PR, Feigin RD. Seizures and other neurologic sequelae of bacterial meningitis in children. *N Engl Med*. 1990; 323: 1651-7.
 18. Viallon A, Botelho-Nevers E, Zeni F. Clinical decision rules for acute bacterial meningitis: current insights. *Open Access Emergency Medicine* 2016; 8: 7-16.
 19. Durand ML, Calderwood SB, Weber DJ, et al. Acute bacterial meningitis in adults. A review of 493 episodes. *N Engl J Med*. 1993; 328 (Suppl 1): 21-8.
 20. Brouwer MC, Thwaites GE, Tunkel AR, Van De Beek D. Dilemmas in the diagnosis of acute community-acquired bacterial meningitis. *Lancet*. 2012; 380 (9854): 1684-92.
 21. Ranković A, Vrbić M, Jovanović M, Popović-Dragonjić L, Đorđević-Spasić M. Meningeal syndrome in the practice of Infectious diseases. *Acta Medica Medianae* 2017; 56(2): 32-7.
 22. Janković Lj, Pantović V, Damjanov V. Korelacija između klime i bakterijskog meningitisa. *Medicus* 2006;7 (1):29-31.