ORIGINAL ARTICLE

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COMPARATIVE ANALYSIS OF BACTERIAL NEUROINFECTIONS BEFORE AND DURING THE COVID-19 PANDEMIC

P. Argirova[1], Y. Kalchev[2,3,4], A. Yaneva[5], O. Boykinova[1,6]

[1]Department of Infectious Diseases, Parasitology and Tropical Medicine, Faculty of Medicine, Medical University – Plovdiv, Bulgaria
[2]Department of Medical Microbiology and Immunology "Prof. Dr. Elisey Yanev", Faculty of Medicine, Medical University – Plovdiv, Bulgaria
[3]Laboratory of Microbiology, "Sveti Georgi" University Hospital, Plovdiv, Bulgaria
[4]Research Institute, Medical University – Plovdiv, Bulgaria
[5]Department of Medical Informatics, Biostatistics, and eLearning, Faculty of Public Health, Medical University – Plovdiv
[6]Clinic of Infectious Diseases, "Sveti Georgi" University Hospital, Plovdiv, Bulgaria

Abstract. *Bacterial meningitis and meningoencephalitis are severe diseases that can be fatal or lead to permanent disability in survivors despite the availability of antibiotic therapy. After the emergence of SARS-CoV-2, changes in morbidity, hospitalizations and etiology have been observed in some countries.* ***Aim:*** *The aim of this analysis was to compare the epidemiological and clinical characteristics of patients with bacterial neuroinfections before and during COVID-19.* ***Materials and methods:*** *The study included 126 patients with bacterial neuroinfections, treated at the Clinic of Infectious Diseases, "Sveti Georgi" Univeristy Hospital in Plovdiv, during two equal periods – from January 2016 to September 2019 (shortly before COVID-19), and from March 2020 to December 2023 (during COVID-19), respectively. Clinical and epidemiological data, laboratory, microbiological, and molecular tests, as well as imaging techniques, were used.* ***Results:*** *90 patients with bacterial neuroinfections were hospitalized during the pre-COVID-19 period, whereas hospitalizations were only 36 during the COVID-19 period. In addition, seasonal, gender, and age distribution differences were observed. The etiology was similar in both observational periods, with the most common agents being S. pneumoniae, Staphylococcus spp., and L. monocytogenes. Mortality rate was similar (33.3% vs. 37.1%, respectively), but differences in terms of etiology were observed.* ***Conclusion:*** *The significant reduction of bacterial neuroinfections during the COVID-19 period is probably due to the public prevention and control measures introduced at the beginning of the pandemic. The emergence of new pathogens and the measures that society takes towards fighting them can have an impact on the epidemiology, clinical course, and prognosis of other diseases that are already known to humanity.*

Key words: *bacterial meningitis, neuroinfection, COVID-19 pandemic*

Corresponding author: *Petya Argirova, Department of Infectious Diseases, Parasitology and Tropical Medicine, Faculty of Medicine, Medical University – Plovdiv, Bulgaria, email: petia_med6@abv.bg*

ORCID: *0000-0003-2223-9058*

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INTRODUCTION

Bacterial meningitis and meningoencephalitis are severe neurologic diseases that can be fatal or lead to permanent disability in survivors, even with antibiotic therapy. *S. pneumoniae*, *H. influenzae*, and *N. meningitidis*, usually transmitted through respiratory droplets and secretions, are leading causes of invasive diseases, including bacteremic pneumonia, meningitis, sepsis, and bacterial superinfections after viral respiratory infections [1, 2, 3].

SARS-CoV-2 caused a global pandemic in 2020, with millions of people infected and a significant number of fatal outcomes. In Bulgaria, the first cases of COVID-19 were registered in March 2020. The high incidence of COVID-19 and effective preventive measures had an impact on the spread and incidence of other infectious diseases, including central nervous system infections.

Some studies have reported a significant decline in neuroinfections since the emergence of SARS-CoV-2. Changes in the incidence, rate of hospitalizations, and etiological structure of neuroinfections have been observed in a number of countries. A prospective analysis from 26 countries (Belgium, Brazil, Canada, China, Czech Republic, Denmark, England, Finland, France, Germany, Hong Kong, Iceland, Ireland, Israel, Luxembourg, Netherlands, New Zealand, Northern Ireland, Poland, Scotland, South Africa, South Korea, Spain, Sweden, Switzerland, Wales) on six continents indicates a significant and sustained reduction in invasive diseases due to *S. pneumoniae*, *H. influenzae* type b and *N. meningitidis* in 2020, coinciding with the introduction of COVID-19 containment measures [4]. A retrospective multicenter study in Germany reported a significant decrease in cases of pneumococcal meningitis, but also of viral meningitis and encephalitis, mainly enterovirus, in 2020 [5]. A Polish study indicated a decrease in the incidence of meningitis and encephalitis in 2020 by up to 63% compared to 2019. In particular, 61% reduction of pneumococcal meningitis and 41% reduction of meningococcal meningitis were recorded. Unexpectedly, cases of meningitis caused by *H. influenzae* type b increased by 20% [6].

The aim of the analysis was to investigate and compare the epidemiology and clinical course of bacterial neuroinfections before and after the emergence of SARS-CoV-2 by analyzing case frequency, age and gender distribution, clinical symptoms and signs, comorbidity, and mortality rate.

MATERIALS AND METHODS

A total of 126 patients with bacterial neuroinfections treated at the Clinic of Infectious Diseases, “Sveti Georgi” University Hospital in Plovdiv, were included. The first observation period (45 months) was before the COVID-19 pandemic, from January 2016 to September 2019. The second observation period (also 45 months) was during COVID-19, from March 2020 to December 2023.

Clinical and epidemiological data, laboratory tests, microbiological and molecular methods, imaging techniques, including brain Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), were used. Statistical data processing was performed using SPSS v.23 software product. The significance level of the null hypothesis was $p < 0.05$.

To identify the pathogens responsible for the disease, multiple microbiological tests were performed. Direct microscopy and cerebrospinal fluid (CSF) culture examination were mandatory for all 126 patients. Multiplex PCR of CSF was performed in a small number of patients (n = 35), depending on its availability. This method was able to identify the most common causative agents for central nervous system infections, including *S. pneumoniae, S. agalactiae, N. meningitidis, L. monocytogenes, H. influenzae*, *E. coli K1, Cytomegalovirus, Herpes simplex virus-1, Herpes simplex virus-2, Human herpes virus 6, Human parechovirus, Varicella zoster virus*, and *Cryptococcus neoformans/gattii*. CSF PCR for Mycobacterium tuberculosis was done in patients who were suspicious of tubercular etiology. Blood cultures were used in the majority of patients. Nasopharyngeal swabs were tested for SARS-CoV-2 by PCR in all patients during COVID (2020-2023).

The inclusion criteria for this study were as follows:

1. Patients must be treated at the Clinic of Infectious Diseases, “Sveti Georgi” University Hospital – Plovdiv, with etiologically verified bacterial meningitis (BM), and/or with clinical data and typical CSF results for BM.

2. The etiological diagnosis was confirmed by CSF culture and/or Multiplex PCR.

3. Only patients with high clinical and CSF suspicion for bacterial etiology were categorized as unidentified cases of BM. Highly suspicious clinical symptoms and signs were fever, headache, vomiting, seizures, meningeal irritation, and altered mental status. CSF indicators included leukocytes over 6×10^9/l with polymorphonuclear predominance, protein over 1.0 g/l, decreased glucose (< 2.2 mmol/l), or decreased CSF/serum glucose ratio (< 0.4).

The exclusion criteria were as follows:

1. Patients with suspected bacterial neuroinfection but refusal of hospital care were not included.

2. Patients with clinical evidence of neuroinfection but no lumbar puncture (LP) performance due to contraindications or patient/relatives' refusal were also not included.

RESULTS

During the period before COVID-19 (2016-2019), 90 patients with BM were hospitalized, whereas during the pandemic (2020-2023), only 36 patients were admitted to the Infectious Disease Clinic. These data show a significant 2.5-fold decrease in the number of hospitalized patients. Figure 1 shows the number of cases of bacterial neuroinfections during both observation periods. There was a sharp decrease in cases during the first two years of the COVID-19 pandemic (2020 and 2021), then a gradual increase began.

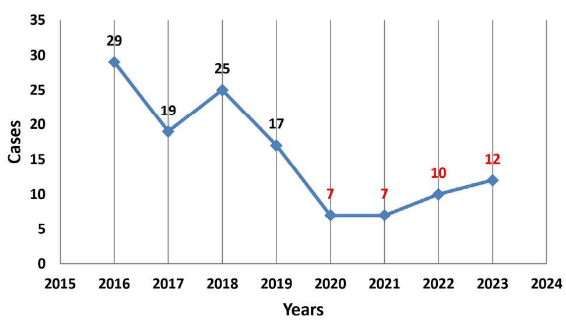

Fig. 1. Cases of bacterial neuroinfections, 2016-2023

The patients' gender distribution data before COVID-19 (n = 90) show that 60% were men and 40% were women. During COVID-19 (n = 36), it was the opposite – 44% were men and 56% were women (Table 1). Despite that, no significant difference was found between the groups before and during COVID-19 (p = 0.12).

Table 1. Gender distribution of BM patients

Gender	Before COVID-19 (n = 90)	During COVID-19 (n = 36)	χ^2	p-value
	N (%)	N (%)	2.520	0.12
Male	54 (60%)	16 (44%)		
Female	36 (40%)	20 (56%)		

The seasonal distribution data of the cases before (n = 90) and during COVID-19 (n = 36) were different. During the first period (2016-2019), most of the cases of bacterial meningitis were reported in winter and spring, with a peak in February and May (Figure 2). However, during COVID-19 (2020-2023), most cases were in summer and autumn, with a peak in August and November (Figure 3).

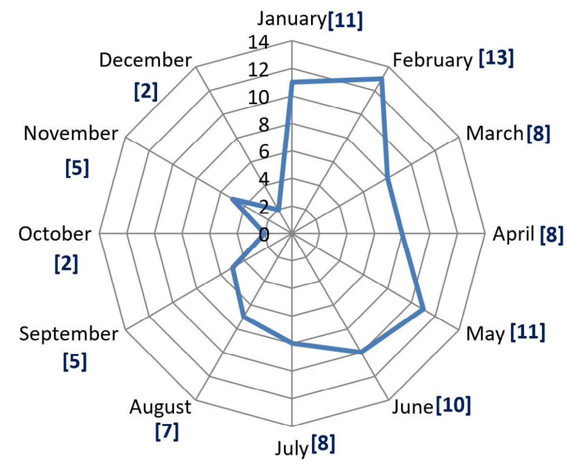

Fig. 2. Seasonal distribution of BM cases in the pre-COVID-19 period, 2016-2019 (n = 90)

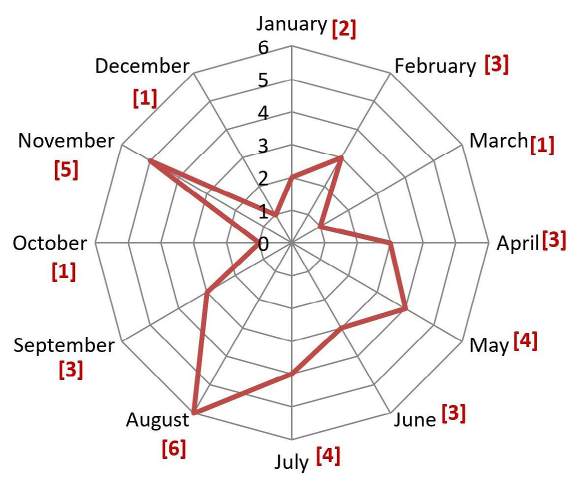

Fig. 3. Seasonal distribution of BM cases during the COVID-19 period, 2020-2023 (n = 36)

Age distribution data of patients with BM before (n = 90) and during COVID-19 (n = 36) are presented in Figures 4 and 5. Before the pandemic, most patients were between 40 and 59 years of age (28.9%) and over 60 years of age (30%). However, during the pandemic, the majority of patients were over 60 years of age (63.9%). Children (persons < 18 years) were 25 (27.8% of all patients in the group) before COVID-19, while during the pandemic, only one child (2.8%) was admitted to the hospital. A statistically significant difference in age distribution was found between the „pre-COVID-19" group (n = 90) and the „during COVID-19" group (n = 36) (p = 0.001).

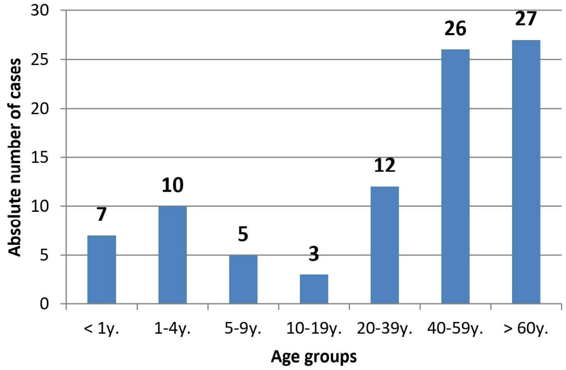

Fig. 4. Age distribution in the "pre-COVID-19" group (n = 90)

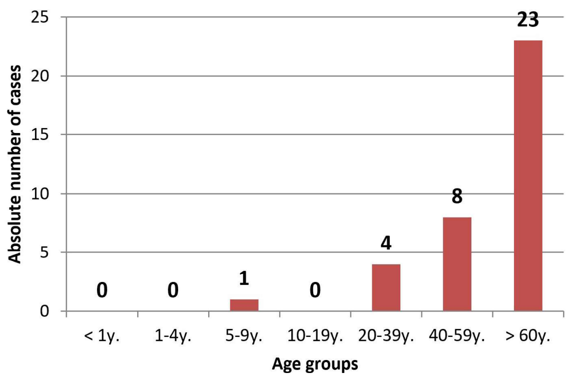

Fig. 5. Age distribution in the "during COVID-19" group (n = 36)

The mean age of patients from the "pre-COVID-19" group was 42.35 years (SD ± 28.08). Our youngest patient was only 16 days old, and the oldest one was 87 years old. The mean age during COVID-19 was 60.39 years (SD ± 18.44), as the minimal age was 9 years and the maximum age was 85.

The etiology of bacterial neuroinfections is presented in Table 2. The most common etiological agent in the "pre-COVID-19" group (2016-2019) was *S. pneumoniae* (18.9% of all BM cases), followed by *Staphylococcus spp*., mainly *S. aureus* (12.3%), *L. monocytogenes* (8.9%), and *N. meningitidis*. Other pathogens have been isolated much less frequently, such as *Streptococcal spp*., *K. pneumoniae, H. influenza, E. faecium*, and *M. tuberculosis*. During the second period, again *S. pneumoniae* was the most common pathogen (19.4%), followed by *S. aureus* (13.9%) and *L. monocytogenes* (11.1%). Single cases due to *M. tuberculosis*, *N. meningitidis*, *H. influenzae*, *E. coli*, and *A. baumannii* were identified. In both groups, a significant proportion of cases were unidentified BM (40% and 39%, respectively).

Table 2. Etiology of bacterial meningitis

Pathogens	Pre-COVID-19 (2016-2019), n = 90		During COVID-19 (2020-2023), n = 36	
	N	%	N	%
Streptococcus pneumoniae	17	18.9%	7	19.4%
Staphylococcus spp	12	12.3%	5	13.9%
Listeria monocytogenes	8	8.9%	4	11.1%
Neisseria meningitidis	5	5.6%	1	2.7%
Streptococcus spp	3	3.3%	0	0
Klebsiella pneumoniae	3	3.3%	0	0
Haemophilus influenzae	2	2.2%	1	2.7%
Enterococcus faecium	2	2.2%	0	0
Echerichia coli	0	0	1	2.7%
Acinetobacter baumannii	0	0	1	2.7%
Mycobacterium tuberculosis	2	2.2%	2	5.6%
Unidentified	36	40%	14	39%
Total	90 100%		36 100%	

A significant proportion of patients have comorbidities. 76.8% of patients from the "pre-COVID-19" group and 80.4% of the "during COVID-19" group had at least one chronic medical condition. Some of the most common comorbidities are analyzed in Table 3. Cardiovascular diseases, malignancy, and diabetes mellitus were more common during the pandemic, compared to the pre-COVID-19 period. Immunosuppressive conditions, including HIV/AIDS or taking immunosuppressive drugs, were not registered during the pandemic period. The difference between groups was statistically significant only for cardiovascular diseases (p = 0.03).

Table 3. Comorbidities in BM patients

Comorbidities	Pre-COVID-19 (n = 90)		During COVID-19 (n = 36)		χ^2	p-value
	N	%	N	%		
Cardiovascular diseases*	35	38.9%	25	69.4%	9.625	0.03
Diabetes mellitus	15	16.7%	11	30.6%	3.029	0.93
Malignancy	7	7.8%	5	13.9%	-	-
Immunosuppression	15	16.7%	0	0	-	-

*Included arterial hypertension, arrhythmias, coronary artery disease, chronic heart failure, cerebrovascular disease

Risk factors for developing bacterial meningitis are shown in Table 4. The frequency of head trauma in the past (8.3%) and CSF leak (5.6%) was higher during the pandemic than during the pre-COVID-19 period, while others, such as splenectomy, previous episode of meningitis, and alcoholism, were absent.

Table 4. Risk factors in BM patients

Risk factors	Pre-COVID-19 (n = 90)		During COVID-19 (n = 36)	
	N	%	N	%
Head trauma	6	6.7%	3	8.3%
CSF leak	3	3.3%	2	5.6%
Splenectomy	2	2.2%	0	0
Previous episode of BM	4	4.4%	0	0
Alcoholism	4	6.2% of adults	0	0

A similar clinical presentation was observed in patients with BM before and during the pandemic (Figure 6). No significant differences were found between groups in terms of fever (n = 0.37), headache (p = 0.84), vomiting (p = 0.17), seizures (p = 0.61), meningeal irritation signs, or altered mental status (p = 0.68).

Severe symptoms usually lead to rapid and timely hospitalization. Most patients were admitted to the hospital within 3 days of clinical onset. During the pandemic, even the proportion of patients who promptly sought medical care (≤ 3 days) was higher than before COVID-19 (56% vs. 49%). There was no significant difference in the duration of the pre-admission period between groups (χ^2 = 0.467, p = 0.79). The mean pre-admission duration was 4.8 days (SD ± 3.5) in the "pre-COVID19" group, and 4.2 days (SD ± 3.5) in the "during COVID-19" group.

The most common concomitant conditions are otogenic diseases like otitis media, mastoiditis, and sinusitis, as well as pneumonia and sepsis (Table 5). Their frequency was similar, and no significant differences were found between groups (p = 0.80). During the pandemic period, two BM patients had coinfection with SARS-CoV-2 (5.6%).

Table 5. Concomitant conditions in the course of BM

Concomitant conditions	Pre-COVID-19 (n = 90)		During COVID-19 (n = 36)	
	N	%	N	%
Otogenic*	24	27.8%	9	25%
Pneumonia	14	16.7%	7	19.4%
Sepsis	11	12.2%	4	11.1%

*otitis media, mastoiditis, sinusitis

The prognosis for BM patients was unfavorable, with a very high mortality rate (Table 6). Mortality was higher in patients during the pandemic than during the pre-COVID-19 period (37.1% vs. 33.3%), but the difference was not significant (p = 0.68). Neurological sequelae in survivors were registered less frequently during the pandemic compared to the pre-COVID period (2.9% vs. 12.2%).

Table 6. Outcomes of BM patients

Outcome	Pre-COVID-19 (n = 90)		During COVID-19 (n = 36)		p-value
	N	%	N	%	
Recovery	49	54.4%	21	60%	0.68
Recovery with sequelae	11	12.2%	1	2.9%	
Death	30	33.3%	13	37.1%	

Table 7 shows the mortality rate according to BM etiology. The mortality is the same in both periods for meningococcal (0%) and listerial meningitis (50%). The lack of fatal outcomes in the pneumococcal meningitis group in the "during COVID-19" group is surprising, while in the "pre-COVID-19" group, the

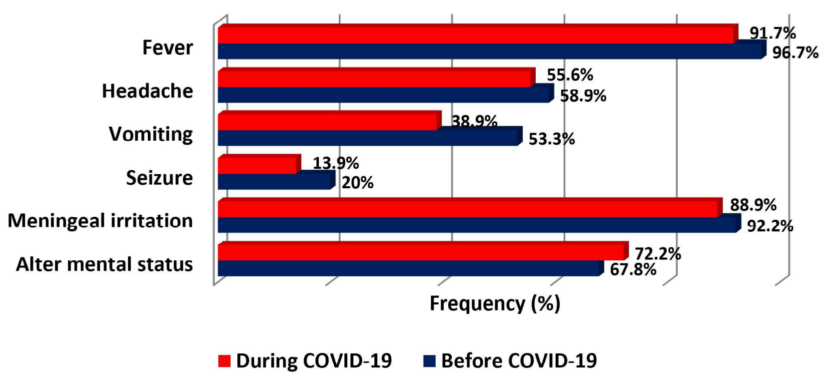

Fig. 6. Clinical presentation in BM patients

Table 7. Mortality according to the BM etiology

Pathogen	Pre-COVID-19 (n = 90)			During COVID-19 (n = 36)		
	Cases	Fatal, N	Fatal, %	Cases	Fatal, N	Fatal, %
Streptococcus pneumoniae	17	6	35.3%	7	0	0
Staphylococcus spp	12	5	41.7%	5	4	75%
Listeria monocytogenes	8	4	50%	4	2	50%
Neisseria meningitidis	5	0	0	1	0	0
Other identified*	12	4	33.3%	5	3	60%
Unidentified	36	11	30.6%	14	5	35.7%

*The group "other identified" in the pre-COVID-19 period included *Streptococcus spp, K. pneumoniae*, *H. influenzae*, *E. faecium*, and *M. tuberculosis*, and during the COVID-19 period – *H. influenzae*, *E. coli, A. baumannii*, and *M. tuberculosis*.

mortality rate was 35.3%. Mortality was extremely high for patients with staphylococcal meningitis, especially during the pandemic (75%).

DISCUSSION

The number of patients suffering from bacterial meningitis varied over the years, but there was an obvious decline during the first two years of the COVID-19 pandemic, when only 7 cases per year were registered in our Clinic of Infectious Diseases. The decrease in cases of bacterial neuroinfections during COVID-19, although being significant (2.5-fold), is probably a temporary phenomenon and will soon reach its baseline levels from before the pandemic. The gender distribution of patients was almost equal during both observation periods. The differences in seasonality of bacterial meningitis are interesting. While during the pre-COVID-19 period, BM cases predominated in winter and spring, during the COVID-19 period, it was exactly the opposite, and most cases were registered in summer and autumn. Why this difference occurred is not particularly clear. This observation is probably coincidental. Also, the number of patients is too low to make any final assumptions, especially for the data during the COVID-19 period.

Our results on age distribution during the pandemic period and the lack of infected children do not correlate with other authors' data. According to this research, cases of BM in children were still reported, even though they were much less frequent [7]. Since most patients with BM during the COVID-19 period are over 60 years old, a significantly higher average age was also found compared to the patient group from the first period (60.39 vs. 42.35 years).

Regarding the changes in etiology, our results for pneumococcal and meningococcal meningitis coincide with *H. influenzae* meningitis in the literature data. Some authors report an increase in the frequency of *H. influenzae* infections [6, 8]. Cases of staphylococcal, listerial infections, and meningitis, caused by other pathogens that are not transmitted by airborne droplets, also decreased during COVID-19, according to our study, while this data was not observed by foreign authors [5]. In general, the etiological structure of BM during the two observation periods remained similar, with the leading causes being *S. pneumoniae, Staphylococcus spp.*, and *L. monocytogenes*.

A significant proportion of our patients have comorbidities that likely complicate the course of acute meningitis and make their treatment and recovery more difficult. The more frequent cardiovascular diseases in patients with meningitis during the COVID period are not surprising, given their age profile compared to the patients from the pre-COVID group. Regarding risk factors for BM, our data were almost similar to the literature [14]. The results on alcoholism were interesting. The absence of alcoholism does not correspond with foreign authors' data, which report an increased frequency of this risk factor in patients with BM during COVID-19. According to Liechi F et al. the frequency of alcoholism was 6.2% in patients with BM from 2006 to 2019, whereas during 2020-2021 it increased to 18% [9]. The results about the similar clinical picture of BM patients from both groups were completely logical and expected. The duration of the pre-admission period is similar in both groups, and its average value during the COVID period is slightly shorter. This shows that despite the pandemic situation, there is no delay in providing medical care to patients with meningitis.

During the COVID-19 pandemic, unfavorable outcomes and increased mortality in BM patients were more frequently reported than in previous years [9, 10]. Our results are similar and show that overall mortality increased from 33.3% to 37.1%. However, data on zero mortality from pneumococcal meningitis during the pandemic differ from those of other authors, who report an increase in mortality, from 18% before COVID-19 to 30% in 2020-2021 [7].

Only two of our patients with BM had SARS-CoV-2 infection as well. One of them had pneumonia and respiratory failure, and the outcome was fatal. Coinfection of bacterial meningitis and COVID-19 is rare. A few case reports on this topic have been described in the literature [11, 12, 13]. Cases of co-infections of

COVID-19 with other infectious diseases with severe course have also been reported [15].

The COVID-19 pandemic has had an impact on the epidemiological characteristics of the patients (incidence, age, and gender distribution), rather than on the clinical course of bacterial meningitis, the presence of concomitant conditions, and complications. Clinicians should not expect any significant differences in patients before and during a pandemic from a clinical point of view. However, in cases of co-infection of bacterial meningitis and acute SARS-CoV-2 infection, a more severe course can be expected, with symptoms and signs of both diseases. Therefore, it is highly recommended that patients, even those with a confirmed infectious disease, be tested for the pandemic disease as well.

Also, our study has some limitations. First of all, it is the small number of patients included, especially during the second observation period. Acute bacterial meningitis is currently a rare disease in our country. In addition, the study is single-center, and patients with meningitis from only one Infectious Disease Clinic in one regional city (Plovdiv) were included. Second, a very small number of patients underwent molecular testing of cerebrospinal fluid by PCR. This is probably the reason for the high proportion of etiologically unidentified bacterial meningitis cases.

CONCLUSION

The significant reduction of bacterial neuroinfections during the COVID-19 period is probably due to the public, preventive, and control measures introduced at the beginning of the pandemic. The emergence of new infectious pathogens and the measures that society takes towards them can have an impact on the epidemiology, clinical course, and prognosis of other diseases that are already known to humanity.

Conflict of Interest Statement: *The authors declare no conflicts of interest related to this work.*

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Ethical statement: *This study has been performed in accordance with the ethical standards as laid down in the Declaration of Helsinki.*

Informed Consent from Participants: *Informed consent was obtained from all participants included in the study.*

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