

The epidemiology of bacterial meningitis in Kosovo

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Abstract

Introduction: The purpose of this study was to present the epidemiologic features of bacterial meningitis in the developing country of Kosovo.

Methodology: Data were collected from active surveillance of bacterial meningitis cases treated at the University Clinical Center of Kosovo in the years 2000 (first post-war year) and 2010.

Results: Meningitis cases in 2000 compared with 2010 showed a 35.5% decline in incidence (from 4.8 to 3.1 cases per 100,000 population) and a decrease in the case fatality rate from 10% to 5%. In children, there was a lower mortality rate (5% versus 2%) and a lower incidence of neurological complications (13% versus 16%) as compared to adults (32% versus 10% and 16% versus 35%, respectively). *Neisseria meningitidis* was the most common pathogen of bacterial meningitis in both study periods. Bacterial meningitis was most prevalent in the pediatric population, and showed an increase in the median age, from three years in 2000 to seven years in 2010. A steady number of bacterial meningitis cases in adults throughout last decade (around 20 cases per year) was recorded.

Conclusions: During the last decade, gradual changes have been observed in the epidemiology of bacterial meningitis that are unrelated to the introduction of new vaccines, but are partly due to the improvement of living conditions.

Key words: bacterial meningitis; neurological complications; outcomes; epidemiology

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Introduction

Despite many new antibacterial agents, bacterial meningitis fatality rates remain high, with reported values between 2% and 30% [1-13]. Furthermore, sequelae, such as epilepsy, mental retardation, or sensorineural deafness are observed in 10%–20% of those who survive [3,4,6,14-17].

The three most common etiologic agents of bacterial meningitis, *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae*, and *Neisseria meningitidis*, account for 90% of reported cases of acute bacterial meningitis in infants and children over four weeks of age [1,10,18,19,20,21,22].

The two most important epidemiologic changes in bacterial meningitis have been the reduction in the incidence of *H. influenzae* meningitis and the emergence of antibiotic-resistant *S. pneumoniae* [11,12,18,21,23-28]. The widespread use of effective Hib conjugate vaccines in 1988 in the United States and in 1996 in Europe caused a dramatic decline in the incidence of *H. influenzae* type B meningitis in children [11,12,18]. Three other control measures (*i.e.*, universal screening and antibiotic prophylaxis of

pregnant women for Group B streptococci [GBS] and the implementation and availability of the *S. pneumoniae* and *N. meningitidis* conjugate vaccines) have likely further decreased the incidence of these meningeal pathogens [19,29]. Since the introduction of the *H. influenzae* type b and *S. pneumoniae* conjugate vaccines to the infant immunization schedule, the peak incidence of bacterial meningitis shifted from children under five years of age to adults [19,20,23,29]. Lastly, the worldwide emergence of multidrug-resistant pneumococci has complicated the empiric therapy of bacterial meningitis [21,23-25]. In Kosovo, only the Hib conjugate vaccine was implemented in 2010. *S. pneumoniae* and *N. meningitidis* conjugate vaccines as well as universal screening for GBS or antibiotic prophylaxis of pregnant women have not yet been introduced in Kosovo. During the last decade, gradual changes have been observed in the epidemiology of bacterial meningitis in Kosovo, unrelated to the introduction of new polysaccharide and conjugate vaccines.

Methodology

Patients and data analysis

Epidemiological data was prospectively analyzed through patient observation and chart review. The causative pathogens and patient outcome of bacterial meningitis cases treated at the University Clinical Center of Kosovo during two study periods were recorded: the first year after the Kosovo war (2000) and in 2010, when the vaccination of children with Hib vaccine was implemented. The incidence of bacterial meningitis over a 10-year period – from 2000 to 2010 – from data collected from active surveillance of patients treated for bacterial meningitis at the Infectious Diseases Clinic in Prishtina (the capital city of Kosovo) was also analyzed. For over 37 years, every child suspected of meningitis throughout Kosovo has been sent to a specialized ward for the treatment of central nervous system (CNS) infections at this facility; the furthest distance from Prishtina is estimated to be under 100 kilometers or a 1.5-hour drive. Data were analyzed by age distribution. Children were categorized into the following age groups: < 1, 1–5 and 6–16 years of age. Adults were categorized into the following age groups: 17–30, 31–50 and > 50 years.

Meningitis definition

The diagnosis of bacterial meningitis was based on World Health Organization (WHO) criteria: clinical symptoms (*e.g.*, fever, meningeal signs), pleocytosis ($> 100/\text{mm}^3$) in cerebrospinal fluid (CSF), and either direct (positive blood or CSF culture) or indirect (positive latex agglutination test or CSF Gram stain) confirmation of bacterial infection. Cases of tuberculous meningitis and neurobrucellosis as well as children younger than one month of age were excluded from the study. Hospital-acquired meningitis cases were defined as cases that acquired bacterial meningitis following neurosurgical procedures or intracranial manipulation.

In the study, epidemiologic data collected from adult and pediatric patients diagnosed with bacterial meningitis were analyzed; the cases were distributed by age groups, gender, and rural or urban location. Patient outcomes were also measured.

Microbiology

All CSF samples were forwarded to a reference laboratory for processing, isolation, and identification of pathogens. The facility used was the Department of Microbiology, National Institute of Public Health of

Kosovo, which operates from 8 a.m. to 2 p.m., Monday through Friday.

These samples were processed and identified following standard operating protocols of the Department of Microbiology, National Institute of Public Health of Kosovo [30].

In addition, the automated Vitek identification system (bioMerieux, Lyon, France) and API strips (bioMerieux, Lyon, France) were used for identification of Gram-negative and Gram-positive bacteria. Serotyping commercial kits for CSF were used to identify isolates of *S. pneumoniae*, *N. meningitidis* serogroups A, B and C, and *H. influenzae* (Slidex Meninge-kit 5, bioMerieux, Lyon, France). Antimicrobial sensitivity testing was conducted using the Kirby-Bauer disk diffusion method according to the National Committee for Clinical Laboratory Standards guidelines and respective AST strips on API and AST VITEK cards (bioMerieux, Lyon, France) [31,32].

In 2000, the etiology of bacterial meningitis cases was confirmed in 43/96 patients (45%); 24/43 cases (56%) were confirmed by CSF Gram stain and 19/43 cases (44%) by CSF and blood cultures. In 2010, the etiology was confirmed in 39/64 patients (61%); 20/39 cases (51%) were confirmed by CSF Gram stain and 19/39 (49%) were confirmed by CSF cultures.

The low pathogen recovery rate was due in part to previous antibiotic treatment and loss of bacterial viability due to the delayed specimen processing resulting from the laboratory's inadequate hours of operation. Instances of previous antibiotic treatment with inadequate doses before being admitted to the clinic were much higher during the second study period (61% versus 40%). In addition, there was no quality control of antibiotics used during both study periods.

Statistical analysis

Statistical analysis was performed using InStat 3 software. Chi-square test and Fisher's exact test were used to compare qualitative variables. All p-values < 0.05 were considered statistically significant.

Results

Between 2000 and 2010, 954 patients were treated for bacterial meningitis at the Clinic of Infectious Diseases in Prishtina, Kosovo, which averages 86 cases per year and an annual incidence of 4.3 cases per 100,000 population. The peak number of cases during the 10-year period was 142 in 2002 (Figure 1).

An average of 108 cases of bacterial meningitis were estimated to have occurred annually in Kosovo between 2000 and 2005, with an annual incidence of 5.4 cases per 100,000 population. Between 2006 and 2010, the number of cases decreased to an average of 61 cases per year with an annual incidence of 3.0 cases per 100,000 (Figure 1). In the first study period, 96 patients (77 children and 19 adults) with bacterial meningitis were hospitalized. Acute neurologic complications developed in 13 patients (13%), and 10 patients died, yielding an overall mortality rate of 10%. In children, a lower mortality rate of four deaths (M = 5%) compared to six (M = 32%) in adults was observed (Table 1).

The highest case fatality rate occurred among infants younger than 3 months of age (three cases) and in adults over 60 years of age (four cases).

In the second study period, 64 patients with bacterial meningitis were hospitalized; 44 were children and were 20 adults. Acute neurologic

complications developed in 14 patients (22%), and the overall mortality rate was 5% (three deaths). A lower mortality rate was recorded in children, with one death (2%), as compared to adults, with two (10%) deaths. The overall mortality rate decreased from 10% in 2000 to 5% in 2010, but the differences were not statistically significant ($p = 0.246$).

The incidence of neurologic complications increased from 13% in the first study period to 22% in the second, but these values lacked statistical significance ($p = 0.244$).

Neurologic complications developed more frequently in adults in both study periods (16% in 2000 and 35% in 2010) as compared to children (13% in 2000 and 16% in 2010) (Table 1).

The incidence of bacterial meningitis decreased from 4.8 cases per 100,000 in 2000 to 3.1 cases per 100,000 in 2010. After a decade, the incidence of bacterial meningitis decreased only among children (Figure 2).

Figure 1. Bacterial meningitis cases by year

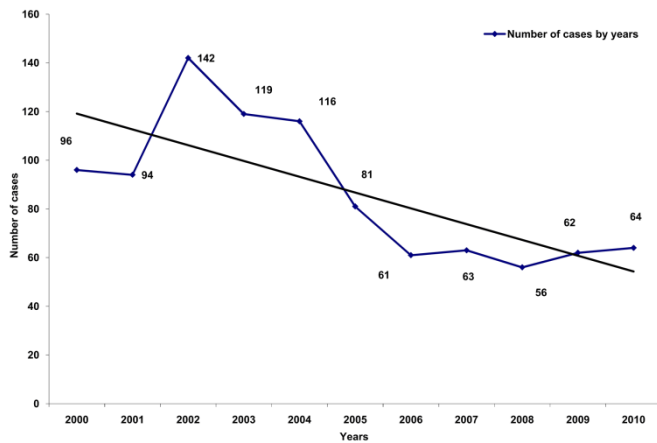


Figure 2. The outcome of bacterial meningitis cases in two study periods

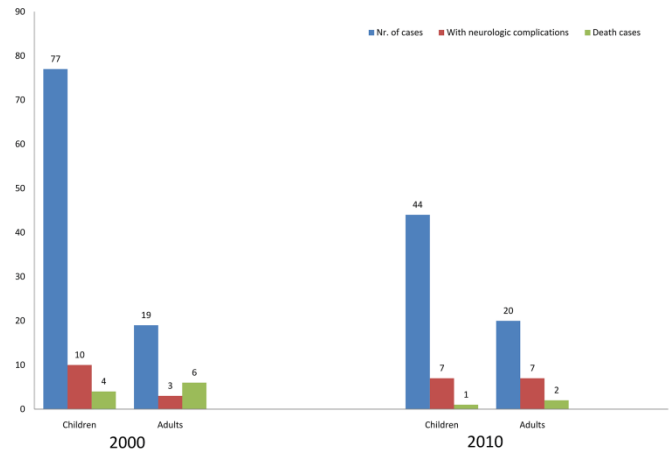


Table 1. The outcome of bacterial meningitis cases in two study periods

	No. of cases	With neurologic complications	Death cases
2000			
Children	77 (80%)	10 (13%)	4 (5%)
Adults	19 (20%)	3 (16%)	6 (32%)
Total cases	96 (100%)	13 (13%)	10 (10%)
2010			
Children	44 (69%)	7 (16%)	1 (2%)
Adults	20 (31%)	7 (35%)	2 (10%)
Total cases	64 (100%)	14 (22%)	3 (5%)

Children between 1 month and 16 years of age accounted for 80% of cases overall in 2000 and for 69% of cases in 2010. The peak incidence in 2000 was in infants (31/77; 40%), compared to increased incidence in children 6–16 years (19/44; 43%) in 2010. The incidence of bacterial meningitis dropped in infants from 40% in 2000 to 23% in 2010, while the incidence in children 6–16 years of age increased from 25% to 43%. No change in the incidence of bacterial meningitis was seen in children 1–5 years of age (35% versus 34%).

A steady number of cases in adults was recorded throughout last decade (approximately 20 cases per year). The incidence of bacterial meningitis in adults peaked in age groups 17–30 and > 50 years in 2000, but only in the > 50-year age group in 2010.

In 2000, the mean age of pediatric cases was 3.2 years (median: 1.5 years), while for adults it was 41 years (median: 36 years). The median age of all bacterial meningitis cases was 3 years (range: 1 month to 68 years).

In 2010, the mean age of bacterial meningitis cases in children was 5.5 years (median: 2.9 years), while for adults it was 45 years (median: 44 years). The median age for all bacterial meningitis cases was 7 years (range: 1 month to 74 years).

The highest numbers of cases were found in males in both children and adults in both study periods, with ratios of 1.2:1 in 2000 and 2.1:1 in 2010; however, differences were not statistically significant ($p > 0.05$). Similarly, patients from urban and rural areas in both study periods showed no statistically significant differences ($p > 0.05$).

In 2000, there were nine cases of hospital-acquired bacterial meningitis (9%) – six cases following neurosurgery, and three cases after implantation of CSF shunt devices. The etiology was confirmed in three of nine cases: *Klebsiella* spp., *S. pneumoniae*, and *Staphylococcus aureus*.

In 2010, there were two cases of hospital-acquired bacterial meningitis (3%) – one case following neurosurgery, and one case after implantation of a CSF shunt device. The etiology was confirmed in both cases: *Pseudomonas aeruginosa* and *Klebsiella* spp.

In 2000, the etiology of all bacterial meningitis cases had microbial confirmation in 43/96 patients (45%). In children, the etiology of bacterial meningitis cases was determined in 34 patients (44%); *N. meningitidis* was the most frequently isolated pathogen (twenty-four cases), followed by *S. pneumoniae* (five cases), Gram-negative bacilli (four cases), and *H. influenzae* type B (one case). In adults, there were 9/19

confirmed cases (47%) due to *N. meningitidis* (four cases), Gram-negative bacilli (three cases), and *S. aureus* (two cases).

In 2010, the etiology of all bacterial meningitis cases was determined in 39/64 (61%) patients. The etiology of pediatric bacterial meningitis cases was proven in 27/44 (61%) to consist of the following: twelve meningococci, five staphylococci, four *H. influenzae*, three pneumococci, and three Gram-negative bacilli isolates. In adults, the etiology of bacterial meningitis cases was confirmed in 12/20 (60%) as the following: eight meningococci, two pneumococci, and two Gram-negative bacilli isolates.

None of children attended kindergarten during the two study periods.

Discussion

During the last decade, advances have been made in the prevention of bacterial meningitis through the introduction of new polysaccharide and conjugate vaccines [12,19,23,29,33]. The implementation of a massive Hib vaccination program in the Western world has nearly eliminated meningitis due to *H. influenzae* type b. In addition, the introduction of conjugate vaccines against *S. pneumoniae* (PCV) is expected to reduce the burden of childhood pneumococcal meningitis significantly [11,12,18,19,34-37]. Although vaccination with a pneumococcal conjugate vaccine is producing herd immunity among adults, the age distribution of meningitis has now shifted to older age groups [19,20,23,29,33,36,37].

Vaccination against the major meningeal pathogens has not been implemented in national immunization programs in Kosovo, with the exception of the Hib vaccine, which was implemented in 2010.

The overall age incidence of bacterial meningitis for Kosovo was 4.8 cases per 100,000 population in 2000, a rate twice as high as those reported from other European countries [38]. A decreased annual incidence of bacterial meningitis from 2006 to 2010 was observed in Kosovo, despite the lack of vaccination during this timeframe. A comparison of the annual incidence in 2000 with 2010 showed a significant decline – 35.5% (from 4.8 to 3.1 cases per 100,000 population). We project a further decline in cases, based on the implementation of the Hib conjugate vaccine in 2010.

Infants and the elderly are the predominant age groups that are predisposed to bacterial meningitis. In Kosovo, after a decade, bacterial meningitis continues to affect children most frequently; the median age of

cases increased from 3 years in 2000 to 7 years in 2010. Children between 1 month and 16 years of age accounted for 80% of cases overall in 2000 and for 69% of cases in 2010. Age-related differences in the declining meningitis incidence were observed. The peak incidence in 2000 – 31/77 (40%) cases were found in infants between two and six months of age. The predilection of the disease to occur in the first years of life is partially explained by the incomplete development of immunity and the loss of maternal protective antibodies [7,39]. After a decade, we recorded a reduction of the incidence in infants from 40% to 23%, while the incidence in the oldest age group (6–16 years) increased from 25% to 43%. The decline in cases among infants in 2010 is most likely attributed to the implementation of the Hib vaccine since none of the vaccinated infants got ill in 2010 and in subsequent years. No change in the incidence of bacterial meningitis was seen in children between 1 and 5 years of age (35% versus 34%) because this age group was not vaccinated in either study period.

Our study showed a predominance of cases found in males among children and adults in both study periods, a finding confirmed in other publications, although the data was statistically insignificant ($p > 0.05$) [40,41]. There may be a real increased risk among males, since males and females are almost equally represented and have equal care-seeking in our country.

There were no statistically significant differences in incidence of meningitis among urban versus rural populations, as they have equal access to health care facilities; the furthest distance from Prishtina is estimated to be under a 1.5-hour drive ($p > 0.05$). We found a decreasing number of hospital-acquired infections in 2010, as infection control practices were implemented to reduce the incidence of hospital-acquired infections in 2010.

N. meningitidis was the most common pathogen of bacterial meningitis in both age groups during both study periods. Our previous report, along with other reports, list meningococcus as the most common cause of bacterial meningitis in young children [12,42-45]. *S. pneumoniae* was reported as the second-most frequent cause of meningitis in several European and sub-Saharan African countries [10,46]. In our study, the second-most frequent cause of bacterial meningitis in children was *S. pneumoniae* in 2000, while in 2010, *S. aureus* was the second-most common pathogen. There were four *H. influenza* cases in 2010, the year when the Hib vaccination was introduced in Kosovo; these patients were not vaccinated.

Our study has one important limitation: the etiology was confirmed only in 43/96 patients (45%) in 2000 and in 39/64 patients (61%) in 2010. Fifty-three patients (55%) in 2000 and 25 patients (39%) in 2010 were treated for probable bacterial meningitis based on WHO criteria: clinical signs and symptoms of meningitis, changes in CSF, and lack of an identifiable bacterial pathogen.

The cases where bacterial confirmation was not obtained is thought to be due to the practice of partial treatment due to administration of antibiotics at the time of specimen collection. In addition, the Department of Microbiology, which is the only one that services our clinical center, is not open daily and does not accept specimens after 2 p.m. The pathogens causing meningitis are fastidious and require immediate processing to optimize recovery and identification. From previous studies, negative cerebrospinal fluid cultures occurred in 11% to 30% of patients with bacterial meningitis [47-62].

Case fatality rates (CFR) remain between 5% and 10% in industrialized countries, and are even higher in the developing world [53-57]. The factors that impact mortality rates include access to primary health care services, the quality of reference laboratories, timely and appropriate medical care and treatment, patient predisposing conditions, and the virulence of the strains [7,40-52,58-62].

The case fatality rate for bacterial meningitis in patients from Kosovo decreased from 10% in 2000 to 5% in 2010, but the differences were not statistically significant.

In Kosovo, the mortality rate in children in the two study periods (5% versus 2%) was comparable to that reported from developed countries [13]. However, the mortality rate was higher among adults in this study when compared to published reports [9], and we observed a decreased case fatality rate (from 32% to 10%) in the second study period. Death occurred predominantly in infants under 3 months and adults over 60 years of age.

Based on a review of the literature, between 10% and 20% of survivors develop permanent sequelae such as epilepsy, mental retardation or deafness and other neurological disabilities; rates between 10% and 20% have been reported in the literature [14-17]. In our study, the detection of early neurologic complications increased from 13% in 2000 to 22% in 2010, perhaps due to the fact that computerized tomography (CT) scanning was performed more frequently during the second study period. Also, the rise in detection of neurologic complications in adults

during the second study period might have also contributed to higher survival rates in this population.

The decline in the incidence of bacterial meningitis in 2010 compared to 2000 may also result from the rational use of preventive and infection control measures in Kosovo. Continuous vaccination and high coverage (> 95%) achieved in populations under 11 years of age (Hib) and under 40 years of age (*N. meningitidis*) may explain not only the decreasing incidence of infection, but the decrease in other age groups (herd immunity) as well [7,63,64].

After a decade, the incidence of bacterial meningitis in Kosovo has decreased only among children, unrelated to the introduction of new polysaccharide and conjugate vaccines. This is partly due to the improvement of living conditions and socio-economic standards a decade after the war in Kosovo. In the first post-war year when people lived in crowded conditions, often in tents, meningitis was more easily transmitted from person to person. Over the past 10 years, living conditions improved, contributing to decreases in incidence and mortality rates. The implementation of robust vaccination programs along with effective antibiotic treatment and advanced health care measures contributed to improved outcomes and lower incidence of bacterial meningitis in developed countries. Future vaccination strategies should be implemented in developing countries as well, to prevent childhood meningitis cases, deaths, and disabilities. Surveillance remains an essential tool in identifying the cases, the etiological agents, and other important epidemiological variables [7].

In conclusion, one decade after the war in Kosovo, the incidence of bacterial meningitis in children has decreased, partly due to improvement of living conditions. We recorded a steady number of bacterial meningitis cases in adults throughout the last decade.

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