The outcome of bacterial meningitis in children is related to the initial antimicrobial therapy

Sadie Namani[1], Remzie Koci[2], Kreshnike Dedushi[3]

[1]Clinic of Infectious Diseases, [2]Pediatric Clinic, and [3]Radiology Institute, University Hospital Center of Kosova, Prishtinë, Kosova

SUMMARY: Namani S, Koci R, Dedushi K. The outcome of bacterial meningitis in children is related to the initial antimicrobial therapy. Turk J Pediatr 2010; 52: 354-359.

Even when highly effective antibiotic therapy is provided to patients, death and long-term disabilities are common outcomes of acute bacterial meningitis (BM) in developing countries. The aim of this study was to analyze how the outcome of disease was related to the initial antimicrobial therapy used to treat the patients. We analyzed 277 children younger than 16 years of age who were treated for BM in the Hospital of Infectious Diseases in Prishtina, Kosova, over a six-year period. Of the 277 children treated for BM, 36.1% of cases were given initial antimicrobial therapy with one antibiotic, 63.2% of cases received two antibiotics and 0.7% of the cases received three antibiotics. Of the 60 patients who had neurologic complications (NC), 50 (28.6%) were treated with two antibiotics, 9 (9%) received one antibiotic and 1 patient was treated with three antibiotics. The antibiotics used most often as monotherapy were penicillin G (63 cases) and ceftriaxone (33 cases). The incidence of NC was higher in children treated with ceftriaxone (NC=22%, mortality [M]=3%) compared with patients treated with penicillin G (NC=3%, M=0). The most commonly used combination of antibiotics was ceftriaxone with chloramphenicol (82 cases) followed by penicillin G with chloramphenicol (63 cases). The incidences of NC and M were higher in children treated with ceftriaxone and chloramphenicol (NC=43%, M=8%) compared to children treated with penicillin G and chloramphenicol (NC=13%, M=3%). The initial treatment of BM with penicillin G did not result in death and was associated with a lower incidence of NC compared with the use of ceftriaxone. The combination of penicillin G and chloramphenicol resulted in a lower incidence of NC and M compared with the combination of ceftriaxone and chloramphenicol.

Key words: bacterial meningitis, treatment, neurologic complication.

Bacterial meningitis (BM) is an emergent disease that has a high mortality rate (M) and is associated with neurologic complications (NC), even if treated early. Although decades have passed since antimicrobial therapy for BM was developed, M continues to be high (from 5-30%) depending on the causative pathogens[1-4]. Due to a lack of vaccination against the three most common BM pathogens (meningococcus, pneumococcus and *Haemophilus influenzae*) in developing countries, BM continues to persist; approximately 70% of cases occur in children younger than five years old[5]. Suspected BM is a medical emergency and therapy should be initiated immediately after the result of a lumbar puncture procedure or immediately after the lumbar puncture itself if the clinical suspicion is very high[6]. Empiric treatment of BM consists of bacterial agent(s) that achieve significant levels in the cerebrospinal fluid (CSF), such as a third-generation cephalosporin with vancomycin. More specific treatments can be instituted when the etiologic agent is identified. The chosen antibiotic should have bactericidal activity in the CSF. In most cases, the initial treatment must be empirical, but nonetheless based on epidemiological knowledge of the most common organisms for each age group and the local antibiotic resistance patterns[5,7]. In a developing country

such as ours, the initial treatment depends on the antibiotics that are available in the hospital.

The aim of the study was to analyze antimicrobial therapy of BM in children, focusing on the outcome of disease related to the initial antimicrobial therapy with one or more antibiotics.

Material and Methods

This work represents a prospective and retrospective study spanning six years. We analyzed 277 children with BM over six years - three years during the war and three years after the war in Kosovo (1997, 1998, 1999, 2000, 2001 and 2002).

We have separately analyzed the outcome of disease in cases that received an initial antimicrobial therapy using one antibiotic and in those that initially received two or three antibiotics. Due to the lack of available antibiotics in our hospital, we could not respect protocols for the empiric treatment of BM in children. During the study, the only antibiotics available were penicillins, aminoglycosides and chloramphenicol. Furthermore, we could not respect protocols for the empiric treatment of BM based on the age group and the suspected pathogen. If the parents could not afford to purchase antibiotics (generally the case), we were forced to use the antibiotics that were available in our ward. On admission, our criteria for the initial treatment with one or more antibiotics were: clinical presentation of illness with prognostic factors for an unfavorable outcome of BM (altered mental state, seizures and neurologic deficit); the possible pathogen; the age group; duration of illness before hospitalization; previous treatment with antibiotics; etiology confirmation and the resistance of meningeal pathogens to antibiotics in our country; the presence of a primary infectious focus; the identification of a community- or hospital-acquired infection (shunt intervention, neurosurgery, etc.); presentation of petechial skin rash; underlying diseases; antibiotics available in the ward; and the material/financial resources of the parents.

Data were analyzed by using the Stata 9.0 program. The statistical parameters analyzed included the structure index, mean and standard deviation. The results were tested using the odds ratio and the relative risk.

Results

Of the 277 children treated for BM, the outcome of disease was favorable in most patients: 72.9% were cured without complications, and 21.6% were cured with NC, while the overall M was 5.4%. The most common NC of MB in children were: subdural effusion (12.6%), recidivant seizures (11.2%), hydrocephalus (2.5%), damage of the VIIIth nerve (1.1%), subdural empyema (0.7%), spinal abscess (0.4%), quadriparesis (0.4%), mental retardation (0.7%), and amaurosis (0.4%).

Initial treatment with two antibiotics was given in 175 cases (63.2%), with one antibiotic in 100 cases (36.1%), and with three antibiotics in 2 cases (0.7%).

Of the 277 children treated for BM, 202 cases (72.9%) were cured without NC: in 89 of these cases (44.0%), the initial treatment was one antibiotic, while two antibiotics were given in 113 of the cases (55.9%) (Table I).

The outcome of BM was significantly worse in patients treated with two or more antibiotics and in those who presented severe clinical form on admission. Of all 60 patients who had NC, 50 (28.6%) were treated with two antibiotics,

Table I. Antimicrobial Treatment of Children with Bacterial Meningitis

	No of cases	%	1 AB	%	2 AB	%	3 AB	%
Cases without neurologic complications	202	.9%	89	32.1%	113	.79%	-	
Cases with neurologic complications	60	.6%	9	3.2%	50	.05%	1	0.36%
Deaths	15	5.4%	2	0.7%	12	4.3%	1	0.36%
Total	277	100%	100	36.1%	175	63.2%	2	0.7%

AB: Antibiotic.

9 (9%) with one antibiotic and 1 with three antibiotics ($p<0.05$) (odds ratio 4.43, 2.114 to 9.520; relative risk 3.221, 1.763 to 6.263).

Fifteen of the MB cases died; two of these cases (0.7%) were given an initial therapy with one antibiotic, 12 cases (4.3%) received two antibiotics, and 1 case (0.4%) was treated with three antibiotics.

Of the 100 cases initially treated with antimicrobial therapy with one antibiotic, 89% were cured without NC, 9% had NC, and M was 2% (Table II). Of the 175 cases initially treated with two antibiotics, 64.6% were cured without NC, 28.9% had NC, and M was 6.8%.

In the two cases where an initial therapy with three antibiotics was provided, one patient was complicated and the other patient died.

In cases initially treated with one antibiotic, we chose penicillin G to treat a suspected meningococcal infection (presentation of petechial skin rash) and ceftriaxone to treat the other suspected pathogens.

An initial treatment with one antibiotic was provided in 36% of the total cases. Penicillin G was provided in 63 cases and ceftriaxone in 33 cases. Significantly more NC occurred in cases treated with ceftriaxone (21.2%) compared with cases treated with penicillin G (3.2%), ($p<0.05$; relative risk 2.676, 1.271 to 3.534; odds ratio 8.54, 1.464 to 64.289) (Table III).

Of the 33 cases initially treated with ceftriaxone, one death due to an unconfirmed etiology (M=3.0) occurred, while no death occurred in children treated with penicillin G as a monotherapy.

Chloramphenicol was given as an initial treatment in two cases (the patients were allergic to penicillins), and these patients were cured without NC. An initial treatment with ampicillin was given in two cases (2%), and one of them was cured without NC, while the other one died.

Patients admitted with a severe clinical form of MB with prognostic factors for an unfavorable outcome (altered mental state, seizures and neurologic deficit) were given an initial antimicrobial therapy with two antibiotics. In cases of suspected meningococcal infection, patients were given an initial therapy with penicillin G and chloramphenicol, while cases that were suspected of other pathogens were given an initial therapy with ceftriaxone and chloramphenicol (Table IV).

Patients given an initial treatment with two antibiotics received a combination of ceftriaxone and chloramphenicol in 82 cases (46.9%), while

Table II. The Outcome of Bacterial Meningitis Based on the Initial Therapy

	1 AB	%	2 AB	%	3 AB	%
Cured without NC	89	89%	113	64.6%	-	
Cured with NC	9	9%	50	28.6%	1	50%
Deaths	2	2%	12	6.8%	1	50%
Total	100	100%	175	100%	2	100%
AB added	11	11%	37	21%	-	-

AB: Antibiotic. NC: Neurologic complications.

Table III. Initial Treatment with One Antibiotic and the Outcome of Bacterial Meningitis

1 AB	No. of cases	%	Cured without NC	%	Cured with NC	%	Deaths	%
Penicillin G	63	63%	61	96.8%	2	3.2%	-	-
Ceftriaxone	33	33%	25	75.7%	7	21.2%	1	3.0%
Chloramphenicol	2	2%	2	100%	-	-	-	-
Ampicillin	2	2%	1	50%	-	-	1	50%
Total cases	100	100%	89	89%	9	9%	2	2%
AB added	11	11%	2	2%	7	78%	2	100%

AB: Antibiotic. NC: Neurologic complications.

Table IV. Initial Treatment with Two Antibiotics and the Outcome of Bacterial Meningitis

2 AB	Total	%	Cured without NC	%	Cured with NC	%		%
CFX+CAF	82	.9%	40	48.8%	35	.7%	7	8.5%
Pen.G+CAF	63	36%	53	84.1%	8	.7%	2	3.2%
AMP+CAF	12	6.9%	10	83.3%	2	.7%	-	-
CFT+CAF	7	4%	4	57.1%	3	.9%	-	-
CFX+AMP	3	1.7%	-	-	1	.3%	2	66.7%
CFX+CLOX	2	1.1%	2	100%	-	-	-	-
CFX+VANC	2	1.1%	2	100%	-	-	-	-
VANC+CAF	1	0.6%	1	100%	-	-	-	-
CLOX+AMP	1	0.6%	1	100%	-	-	-	-
IMIP+VANC	1	0.6%	-	-	1	100%	-	-
CFX+GENT	1	0.6%	-	-	-	-	1	100%
Total cases	175	100%	113	64.6%	50	.6%	12	6.9%
AB added	37	.1%	18	15.9%	18	36%	1	8.3%

AB: Antibiotic. AMP: Ampicillin. CAF: Chloramphenicol. CFT: Cefotaxime. CFX: Ceftriaxone. CLOX: Cloxacillin. GENT: Gentamicin. IMIP: Imipenem. Pen. G: Penicillin G. VANC: Vancomycin.

penicillin G and chloramphenicol were provided in 63 cases (36%).

Neurologic complications occurred in a greater percentage (42.7%) in cases where an initial therapy with ceftriaxone and chloramphenicol was provided, compared to patients given a combination of penicillin G and chloramphenicol (12.7%) ($p<0.001$; odds ratio 5.797, 2.265 to 15.289; relative risk 3.558, 1.876 to 7.14). The M was much higher when the combination of ceftriaxone and chloramphenicol (8.5%) was given, compared with the combination of penicillin G and chloramphenicol (3.2%).
Treatment with three antibiotics was provided in two cases. Ampicillin, chloramphenicol and gentamicin were provided to one patient who was cured with NC, and cefotaxime, chloramphenicol and amikacin were provided to the other patient who died.

After the initial therapy for the treatment of BM in children, we added additional antibiotics in 48 cases (17%) due to the worsening of the clinical presentation, laboratory analysis, cyto-biochemical changes in the CSF, confirmation of pathogens, and verification of resistance to given antibiotics, but seldom due to the etiology. The antibiotics that were added to the treatment regimen of children with BM included ceftriaxone in 6.3% of total cases, trimethoprim-sulfamethoxazole in 4.7% of cases and vancomycin and chloramphenicol in 4% of cases (Table V).

Piperacillin was added in 1.8% of cases, ampicillin, cloxacillin and imipenem in 1.4% of cases, ceftazidime in 0.7% of cases, and

Table V. Antibiotics Added to the Treatment of BM in Children

Antibiotics	Cases with 1 AB	Cases with 2 AB	Total	%
Ceftriaxone	3	14	17	6.3%
Bactrim	-	13	13	4.7%
Vancomycin	1	10	11	4%
Chloramphenicol	9	2	11	4%
Piperacillin	-	5	5	1.8%
Ampicillin	-	4	4	1.4%
Imipenem	1	3	4	1.4%
Cloxacillin	2	2	4	1.4%
Ceftazidime	-	2	2	0.7%
Cefotaxime	-	1	1	0.4%
Total AB added	11 (11%)	37 (21%)	48	17%
Total cases	100	175	277	100%

AB: Antibiotic.

cefotaxime in 0.4% of the total cases. The most frequent causative pathogens of BM in children were: *Meningococcus* (57.2%), *Haemophilus influenzae* (17.7%), *Pneumococcus* (13.7%), *Gram-negative bacilli* (8.1%), *Staphylococcus aureus* (1.6%), and *Streptococcus pyogenes* (0.8%).

During the six years of our study, we did not isolate strains of meningococcus that were resistant to penicillin G, while pneumococcus resulted in penicillin resistance in 5.9% of cases; this pathogen remained sensitive to ceftriaxone in all cases. *H. influenzae* was polysensitive in 92.3% of cases, while it was resistant to ampicillin and chloramphenicol in 4.5% of cases. The highest resistance of pathogens to antibiotics was proven in gram-negative bacillary meningitis. Of the 11 proven cases of gram-negative bacillary meningitis, eight pathogens were sensitive to antibiotics (72.7%), while three cases resulted in polyresistance to antibiotics (27.3%), except sensitivity to imipenem. There was one case of NC (NC=33.3%) and one death from cases resistant to antibiotics (M=33.3%), while there were two cases with NC (NC=25%) and no deaths in cases caused by gram-negative bacilli that were sensitive to antibiotics. Of the three most common BM pathogens in children, there was one death in cases caused by meningococcus (M=1.4%), while there were no deaths in etiology-confirmed cases caused by pneumococcus and *H. influenzae*.

Discussion

Three organisms predominate in causing community-acquired BM in children from Kosova: *Neisseria meningitidis, H. influenzae* and *Streptococcus pneumoniae*. This finding is in line with previous reports in our country and similar to that found in other areas of Southern and Eastern Europe[8,9].

Vaccination against meningeal pathogens has not been implemented into national immunization programs in Kosovo. BM is still a common disease in our country and around 75% of cases occurred in children under five years old. *N. meningitidis* was found to be the leading cause of childhood BM in Kosovo.

Speed in diagnosis, the causative pathogen and the initial antimicrobial therapy represent important factors for the prognosis of BM in children. The speed in diagnosis of BM depends upon the level of primary health care services and the doctors' ability to suspect BM and arrange for immediate transfer to a specialized institution to confirm the diagnosis and initiate the right antimicrobial therapy. Early administration of an optimal antibiotic therapy for BM has been shown to be essential to minimize lethality and morbidity [2,3,10-14]. Recognition of pathogens with increasing resistance to antimicrobial agents is an important factor in selection of an empiric antimicrobial regimen.

During the years of our study, we were unable to respect guidelines for the initial empirical therapy of BM in children due to the lack of antibiotics in our ward. Late and insufficient results of CSF cultures and gram staining made treatment of BM harder, especially in cases with NC.

Risk for developing NC and mortality was very low for cases treated with the initial antimicrobial therapy using penicillin G alone or with chloramphenicol while it was very high in cases treated with ceftriaxone alone or with chloramphenicol. The lower incidence of NC and mortality in cases treated with a combination of penicillin G and chloramphenicol resulted from the fact that meningococcus was the most frequent cause of those cases, while cases treated with a combination of ceftriaxone and chloramphenicol were caused by other pathogens.

The higher incidence of NC and mortality in cases initially treated with two antibiotics was due to the presentation of severe clinical forms on admission with the presence of factors that indicated a poor outcome.

Antibiotic resistance among gram-positive pathogens was low while it was high among gram-negative bacilli. In developing countries such as ours with an unproven resistance of meningococcus to antibiotics, we recommend the initial treatment with penicillin G only in cases suspected of meningococcus that present without a severe clinical form on admission.

With unproven resistance of *H. influenzae* to third-generation cephalosporins, ceftriaxone is the drug of choice for treatment of *H. influenzae* type b (Hib) BM in our country.

With low resistance of pneumococci to penicillin

and unproven resistance to third- generation cephalosporins, ceftriaxone remains the drug of choice for treatment of pneumococcal meningitis.

The high level of resistance to antibiotics of gram-negative bacilli, especially to third-generation cephalosporins, necessitates the appropriate choice of antibiotic with the purpose of reducing mortality and the incidence of NC in BM in children. The implementation of protocols for the empiric treatment of BM is the goal of our future treatments in children in order to reduce the incidences of NC and mortality[15].

Vaccines against meningeal pathogens have been implemented into national immunization programs successfully around the world. Progress needs to be made in order to get these highly effective vaccines in developing countries as well.

In conclusion, our criteria for the initial antimicrobial therapy of BM in children with one or two antibiotics with respect to the factors that influence the outcome of BM (possible pathogens, age group, hospital- or community-acquired infection, clinical presentation of the disease, resistance to antibiotics, antibiotics available in the ward, and the material/financial resources of parents) corresponded with the outcome of BM in our cases.

Acknowledgments

We thank the personnel of the Clinic of Infectious Diseases of Prishtina for their support during this study.

REFERENCES

1. Aronin SI, Peduzzi P, Quagliarello VJ. Community-acquired bacterial meningitis: risk stratification for adverse clinical outcome and effect of antibiotic timing. Ann Inter Med 1998; 129: 862-869.
2. Durand ML, Calderwood SB, Weber DJ, et al. Acute bacterial meningitis in adults. A review of 493 episodes. N Engl J Med 1993; 328: 21-28.
3. Quagliarello VJ, Scheld WM. Treatment of bacterial meningitis. N Engl J Med 1997; 336: 708-716.
4. Kaplan SL, Woods CR. Neurologic complications of bacterial meningitis in children. Curr Clin Top Infect Dis 1992; 12: 37.
5. Friedland IR, Klugman KP. Failure of chloramphenicol therapy in penicillin-resistant pneumococcal meningitis. Lancet 1992; 339: 405.
6. Meadow WL, Lantos J, Tanz RR, Mendez D, Unger R, Wallskog P. Ought 'standard care' be the 'standard of care'? A study of the time to administration of antibiotics in children with meningitis. Am J Dis Child 1993; 147: 40.
7. El Bashir H, Laundy M, Booy R. Diagnosis and treatment of bacterial meningitis. Arch Dis Child 2003; 88: 615-620.
8. Luca V, Gessner BD, Luca C, et al. Incidence and etiological agents of bacterial meningitis among children <5 years of age in two districts of Romania. Eur J Clin Microbiol Infect Dis 2004; 23: 523-528.
9. Ceyhan M, Yildirim I, Balmer P, et al. Etiology of childhood acute bacterial meningitis, Turkey. Emerg Inf Dis 2008; 14: 1089-1096.
10. Wenger JD, Hightower AW, Facklam RR, Gaventa S, Broome CV. Bacterial meningitis in the United States, 1986: report of a multistate surveillance study. The Bacterial Meningitis Study Group. J Infect Dis 1990; 162: 1316–1323.
11. Bohr V, Hansen B, Jessen O, et al. Eight hundred and seventy-five cases of bacterial meningitis. Part I of a three-part series: clinical data, prognosis, and the role of specialised hospital departments. J Infect 1983; 7: 21–30.
12. Spanjaard L, Bol P, de Jong MC, Zanen HC. Bacterial meningitis in 366 children in the Netherlands, 1982–1983. Epidemiology and antibiotic therapy. J Antimicrob Chemother Tijdschrift Kindergeneeskunde 1986; 54: 1–8.
13. Bryan CS, Reynolds KL, Crout L. Promptness of antibiotic therapy in acute bacterial meningitis. Ann Emerg Med 1986; 15: 544–547.
14. Strang JR, Pugh EJ. Meningococcal infections: reducing the case fatality rate by giving penicillin before admission to hospital. Br Med J 1992; 305: 141–143.
15. Talan DA, Hoffman JR, Yoshikawa TT, Overturf GD. Role of empiric antibiotics prior to lumbar puncture in suspected bacterial meningitis: state of the art. Rev Infect Dis 1988; 10: 365.