Causative pathogens of bacterial meningitis in children and their susceptibility to antibiotics

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Abstract

Bacterial meningitis is an emergent disease that is characterized by a high mortality rate and is associated with neurological complications, even when treated early. The aim of this study was to analyze how the outcome of bacterial meningitis in children is influenced by the identity and antibiotic susceptibility of the causative pathogens. Methodology: We have retrospectively analyzed the outcome of 124 culture-proven cases of bacterial meningitis in children treated during a six-year period (1997-2002). Results: Out of 124 culture-proven cases of bacterial meningitis, neurological complications occurred in 36 cases (29.03%), and the overall mortality rate was 2.41% (three cases of death). The most common pathogens associated with bacterial meningitis in children were N.meningitidis (n=71, 57.25%), H. influenzae type B (n=22, 17.74%), S. pneumoniae (n=17, 13.70%) and gram-negative bacilli (n=11, 8.87%). The highest incidence of neurological complications occurred in cases caused by H. influenzae (relative risk 2.44, CI 95%). Out of 124 isolated pathogens, 95.16% of strains were susceptible to antibiotics, while only 4.83% were multiresistant to antibiotics. Conclusion: Although the incidence of neurological complications in culture-proven cases of bacterial meningitis was high, the antimicrobial resistance of causative pathogens was very low in children.

INTRODUCTION

Even when patients are treated with highly effective antibiotic therapies, death and long-term disabilities are common outcomes of acute bacterial meningitis (BM). Suspected BM is considered a medical emergency, and therapy should be initiated immediately after the results of a lumbar puncture procedure are obtained, or even immediately after the lumbar puncture itself if the clinical suspicion is very high 1,2. Empiric treatment of BM involves applying an antibacterial agent(s), such as a third-generation cephalosporin with vancomycin, to the cerebro-spinal fluid (CSF) in substantial levels 3,4. 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 5,6,7,8. The identification of BM pathogens, and their sensitivity to antibiotics, may help transition empirical therapies into pathogen-specific therapies 9.

The aim of this study was to analyze how the outcome of bacterial meningitis in children is influenced by the identity and antibiotic susceptibility of the causative pathogens.

PATIENTS AND METHODS

Our study was observational and retrospective. We analyzed 124 culture-confirmed cases (44.76%) out of 277 cases of BM in children under 16 years of age treated during a six-year period (1997-2002) in the Clinic of Infectious Diseases in Prishtina at the University Clinical Center of Kosovo. We have analyzed the relationship between the outcome of the disease and the identity and antibiotic susceptibility of the causative pathogens. The antimicrobial susceptibility was determined using the disk diffusion method according to the recommendations of the Clinical Laboratory Standard Institute (formerly the NCCLS).

STATISTICAL ANALYSIS

Data were analyzed using the Stata 9.0 program. Statistical significance was evaluated using the relative risk (RR) test with confidence interval of 95%.

RESULTS

During a six-year study period, the causative pathogens of 124 culture-proven cases of pediatric bacterial meningitis cases were as follows: N.meningitidis, 71 cases (57.25%); H.influenzae type B (Hib), 22 cases (17.74%); S.pneumoniae, 17 cases (13.70%); gram-negative bacilli, 11

cases (8.87%); S. aureus, 2 cases (1.61%) and S. pyogenes, 1 case (0.80%)(Table 1).

Figure 1

Table 1. The causative pathogens of BM in children according to age groups

Causative pathogens	0-1m	2-11m	1-2y	3-5y	6-10y	11-16y	Total	%	NC	%	Cases of Death	%
N.meningitidis	-	21	16	19	12	3	71	57.25	15	21.12	1	1.40
H.influenzae	-	13	2	3	2	2	22	17.74	11	50.00	-	-
S.pneumoniae	-	5	4	4	2	2	17	13.70	5	29.41	-	-
Gram-negative bacilli	3	4	2	1	1	-	11	8.87	3	27.27	1	9.09
S.aureus	-	-	-	1	-	1	2	1.61	2	100	-	-
S.pyogenes	1	-	-	-	-	-	1	0.80	-	-	1	100
Total cases	4	43	24	28	17	8	124	100	36	29.03	3	2.41

Out of 124 culture-proven cases of BM, neurological complications (NC) occurred in 36 cases (NC=29.03%), while the overall mortality (M) rate was 2.41% (three cases of death).

The highest incidence of NC occurred in cases caused by H.influenzae (50%)[relative risk 2.44, (1.65-5.12), CI 95%], followed by S. pneumoniae (29.14%)[relative risk 1.01, (0.38-2.68), CI 95%], gram-negative bacilli (27.27%)[relative risk 0.91, (0.25-3.26), CI 95%] and N.meningitidis (21.12%)[relative risk 0.65, (0.43-0.99), CI 95%]. NC occurred in both cases caused by S.aureus [relative risk 2.97, (1.66-5.30), CI 95%](Table 2).

Figure 2

Table 2. Neurological complications of BM according to causative pathogens

Causative pathogens	Causative pathogens	N° of patients	Neurol. complications	%	Relative risk (95%CI)
Meningococcus	Yes	71	15	21.12	0.65 (0.43 – 0.99)
	No	53	21	39.62	
Pneumococcus	Yes	17	5	29.41	1.01 (0.38 – 2.68)
	No	107	31	28.97	
H.influenzae	Yes	22	11	50.00	2.44 (1.65 – 5.12)
	No	102	25	24.50	
Staphylococcus aureus	Yes	2	2	100	2.97 (1.66 to 5.30)
	No	122	34	27.86	
Gram negative bacilli	Yes	11	3	27.27	0.91 (0.25 – 3.26)
	No	113	33	29.20	

Of 71 cases of meningococcal meningitis, NC occurred in 15 cases (21.12%)[relative risk 0.65, (0.43-0.99), CI 95%], with one case of death (M=1.40%).

Antimicrobial susceptibility testing revealed that meningococci were susceptible to penicillin in the cases of all but one isolate (1997) that showed intermediate resistance; ultimately, this case was successfully treated using high doses of penicillin. All 15 cases of meningococcal meningitis that resulted in the development of NC were susceptible to each of the antibiotics tested.

H.influenzae was confirmed as a causative pathogen in 22 cases of BM; no cases of death were observed, though NC occurred in 11 of the cases [relative risk 2.44, (1.65 – 5.12), CI 95%]. Strains of H.influenzae were susceptible to antibiotics in all but one isolate (1999) that was susceptible to cephalosporins but resistant to ampicillin and chloramphenicol (R=4.54%). All 11 cases of H.influenzae BM that developed NC were susceptible to antibiotics.

Of the 17 cases caused by S. pneumoniae, there were no observed cases of death, while NC occurred in five cases [relative risk 1.01), (0.38-2.68), CI 95%]. Strains of pneumococci were susceptible to antibiotics in the cases of all but one isolate (1998), which was resistant to penicillin but susceptible to cephalosporins (R=5.88%). Of the five cases of pneumococcal meningitis that developed NC, four cases were susceptible to penicillin and cephalosporins.

S.aureus was methicillin susceptible in one case but methicillin resistant and vancomycin susceptible in the other case. Both cases caused by S. aureus developed subdural empyema.

Gram-negative bacilli (n=11) were susceptible to antibiotics in eight cases, while three cases were resistant to all antibiotics except carbapenems (R=27.27%). Of the three cases that showed multiresistance to antibiotics, one patient developed NC, and the other patient died (treated with the initial ceftriaxone antimicrobial therapy). Of the three cases that developed NC, two were susceptible to antibiotics.

Of the 124 isolated pathogen agents, 118 strains (95.16%) were susceptible to antibiotics and NC developed in 33 cases (27.96%), while there were 2 observed cases of death (1.69%). Only six strains (4.83%) were multiresistant to antibiotics; of these, three cases developed NC (50%), and one case of death was observed (16.66%). The causative agents of cases in which death occurred were N.meningitidis (susceptible to antibiotics), S. pyogenes (susceptible to antibiotics) and K.pneumoniae (resistant to antibiotics).

For all etiologically-proven cases of BM, the therapy given depended on the results of susceptibility tests of proven pathogens to antibiotics.

DISCUSSION

Three primary organisms are involved in causing community-acquired bacterial meningitis in children from Kosova: N. meningitidis, H.influenzae and S. pneumoniae.

This finding is in line with previous reports in our country and similar to those observed in other areas of Southern and Eastern Europe 17,18. In countries where routine vaccination is available, the implementation of a H.influenzae type B vaccine, universal screening and antibiotic prophylaxis of pregnant women for Group B streptococci as well as the implementation and availability of the S. pneumoniae and N. meningitidis conjugate vaccines are the leading factors associated with decreased incidence of bacterial meningitis 19,20. Vaccination against meningeal pathogens has not been integrated into national immunization programs in Kosovo. BM is still a common disease in the country, and roughly 75% of cases occur in children under the age of five years. N. meningitidis was found to be the leading cause of childhood bacterial meningitis in Kosovo. The mortality associated with BM in children from Kosova has decreased from 4.5% in 1997 to 2.0% in 2002, while the incidence of NC increased from 22.7% to 32.6% during the same time period. The overall mortality rate of BM in children from Kosovo was 5.4%, while for etiologically-proven cases it was 2.4%, a rate similar to those reported in many developing countries 21,24.

The speed of diagnosis, the identity of the causative pathogen and the initial antimicrobial therapy delivered 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 ability of doctors to correctly diagnose BM and immediately transfer patients to specialized institutions for confirmation of the diagnosis and initiation of appropriate antimicrobial therapies. The prognosis is worsened with a delay in management, and the lethality of this disease and frequency of sequelae among those surviving remain substantial 10,11,12,13,14,22. Early administration of optimal antibiotic therapies for bacterial meningitis has been shown to be essential in minimizing lethality and morbidity 10,15,16, 23,25,26. Recognition of pathogens with increasing resistance to antimicrobial agents is an important factor in selection of empiric antimicrobial regimens. In a developing country like Kosovo, the shortage of antibiotics in hospitals makes it difficult to follow guidelines for the initial empirical therapy of children with bacterial meningitis. Late and insufficient results of CSF cultures and gram staining make treatment of BM more difficult, particularly in cases with neurological complications. The implementation of protocols for the empiric treatment of BM to reduce the mortality rate and the incidence of neurologic complications is the goal of our future treatments of children 15.

In the cases presented here, antibiotic resistance was found to be low among gram-positive pathogens but high among gram-negative bacilli; however, the small sample size should be considered when interpreting these results. Although meningococcal strains with decreased susceptibility to penicillin have been reported worldwide since 1985, only one isolate in Kosovo was documented that was intermediately resistant (1997); ultimately, this case was successfully treated with high doses of penicillin 27-36. Therefore, for children with obvious meningococcal diseases and with no proven resistance to antibiotics, penicillin is the drug of choice. Given that resistance of H.influenzae to third-generation cephalosporins is unproven, ceftriaxone is the drug of choice for treatment of H.influenzae BM in Kosovo. Therapy for meningitis caused by the pneumococcus has recently been modified according to current pneumococcal susceptibility patterns 3,4,9,37,38. With the low resistance of pneumococci to penicillin and the unproven resistance to third generation of cephalosporins, ceftriaxone remains the drug of choice for treatment of pneumococcal meningitis. High levels of resistance to antibiotics against gram-negative bacilli, particularly to third-generation cephalosporin, illustrates the importance of appropriate antibiotic choice in reducing mortality and the incidence of NC of BM in children. Vaccines against meningeal pathogens have successfully been implemented into national immunization programs around the world. Progress needs to be made to get these highly effective vaccines to developing countries as well.

CONCLUSION

Although the incidence of neurological complications of culture proven cases of bacterial meningitis was high, the antimicrobial resistance of causative pathogens was very low in children.

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