International Journal of Infectious Diseases 17 (2013) e707–e713

Contents lists available at SciVerse ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

# Association of treatment for bacterial meningitis with the development of sequelae

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ARTICLE INFO

*Article history:*
Received 18 September 2012
Received in revised form 25 January 2013
Accepted 6 February 2013

**Corresponding Editor:** Eskild Petersen, Aarhus, Denmark

*Keywords:*
Bacterial meningitis
Child
Prognosis
Sequelae
Treatment

SUMMARY

*Background:* Bacterial meningitis continues to be a serious, often disabling infectious disease. The aim of this study was to assess the possibility that treatment influences the development of sequelae in childhood bacterial meningitis.

*Methods:* Two thousand four hundred and seventy-seven patients aged 1 month to 14 years with acute bacterial meningitis over a 32-year period were enrolled in the study. Data were collected prospectively from the Meningitis Registry of a tertiary university teaching hospital in Athens, Greece. Treatment was evaluated through univariate and multivariate analysis with regard to sequelae: seizure disorder, severe hearing loss, ventriculitis, and hydrocephalus.

*Results:* According to the multinomial logistic regression analysis, there was evidence that penicillin, an all-time classic antibiotic, had a protective effect on the occurrence of ventriculitis (odds ratio (OR) 0.17, 95% confidence interval (CI) 0.05–0.60), while patients treated with chloramphenicol had an elevated risk of ventriculitis (OR 17.77 95% CI 4.36–72.41) and seizure disorder (OR 4.72, 95% CI 1.12–19.96). Cephalosporins were related to an increased risk of hydrocephalus (OR 5.24, 95% CI 1.05–26.29) and ventriculitis (OR 5.72, 95% CI 1.27–25.76). The use of trimethoprim/sulfamethoxazole increased the probability of seizure disorder (OR 3.26, 95% CI 1.08–9.84) and ventriculitis (OR 8.60, 95% CI 2.97–24.91). Hydrocortisone was associated with a rise in hydrocephalus (OR 5.44, 95% CI 1.23–23.45), while a protective effect of dexamethasone (OR 0.82, 95% CI 0.18–3.79) was not statistically significant.

*Conclusions:* Current study findings suggest that the type of antimicrobial treatment for childhood bacterial meningitis may influence in either a positive or a negative way the development of neurological sequelae.



## 1. Introduction

Acute bacterial meningitis is an infection of the central nervous system (CNS), often disabling, resulting in 170 000 deaths worldwide annually.[1] It is well known that the mortality of untreated meningitis approaches 100%. Nevertheless, since the advent of antimicrobial therapy it has become a curable disease. The first antibiotics that were used successfully for the treatment of bacterial meningitis during World War II were sulfonamide and penicillin. In the following decades a range of antimicrobials became available, including ampicillin, chloramphenicol, ceftriaxone, cefotaxime, and more recently vancomycin.[2] Due to increasing resistance to penicillin and cephalosporins, guidelines for the empirical therapy of bacterial meningitis differ according to the local prevalence of antimicrobial resistance. Third-generation cephalosporins may be used as a first choice for bacterial meningitis beyond the neonatal period in areas of low prevalence of bacterial resistance to cephalosporins. However, a combination of vancomycin and third-generation cephalosporin is increasingly preferred and is certainly the recommended treatment in areas with reported penicillin resistance or cephalosporin-resistant bacterial strains.[3] Adjuvant corticosteroids are recommended, however the benefit of their use in the treatment of bacterial meningitis in children remains unclear. Moreover, advances in diagnostic techniques and critical care services have further contributed to an improved outcome in acute bacterial meningitis. Nevertheless, despite huge progress in the care provided, bacterial meningitis is still a source of substantial morbidity. Between 10% and 20% of survivors develop permanent sequelae such as epilepsy, mental retardation, or hearing impairment.[4] The long-term

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http://dx.doi.org/10.1016/j.ijid.2013.02.009

outcome, including functional and behavioral abilities, in children who have suffered bacterial meningitis beyond the age of 6 months has been investigated, with some evidence of a possible impact.[5] Several risk factors have been related to the development of sequelae, such as the causative organism, age, gender, duration of illness before admission, physical examination findings at admission (depressed level of consciousness, focal neurologic deficits, convulsions, absence of petechiae), laboratory findings (low cerebrospinal fluid (CSF) glucose, high CSF protein, positive blood culture), etc.[6–9] The effectiveness and safety of the various types of therapy in patients with acute bacterial meningitis have also been evaluated.[4,10–12] The aim of our study was to assess the possibility that the type of treatment is a risk factor for sequelae in childhood bacterial meningitis by using data from the Meningitis Registry.

## 2. Materials and methods

### 2.1. Study population

We used data from the Meningitis Registry of the Infectious Diseases Department of Agia Sofia Children's Hospital in Athens, Greece. The study population consisted of children admitted with acute bacterial meningitis to this tertiary hospital from 1974 to 2005. For practical reasons the study was divided by date of admission into three time-periods: period A (1974–1984), period B (1985–1994), and period C (1995–2005); period C represents the time after the introduction of the conjugate *Haemophilus influenzae* type b (Hib) vaccine. Cases were patients aged 1 month to 14 years with clinical and laboratory findings consistent with acute bacterial meningitis. Children with recurrent or tuberculous meningitis were excluded from the analysis. A registry form was completed for each case upon discharge of the patient, and follow-up visits were made for up to 3 months after discharge. The detailed methodology concerning the Meningitis Registry, including study setting, data collection, inclusion and exclusion criteria, and case definitions, have been described elsewhere.[13,14]

### 2.2. Definitions

'Treatment' included parenteral administration of one or more of the following antibiotics: ampicillin, penicillin, cephalosporins (cefotaxime, ceftriaxone, ceftazidime), gentamicin, chloramphenicol, trimethoprim/sulfamethoxazole, and sulfonamide. 'Adjuvant corticosteroid therapy' was defined as the receipt of dexamethasone or hydrocortisone intravenously on the first day of hospitalization. 'Sequelae' was defined as the presence of severe hearing loss, ventriculitis, hydrocephalus, or seizure disorder during a follow-up period of 3 months. The rate of sequelae was estimated among survivors. The term 'severe hearing loss' was applied to a hearing threshold of $>$80 dB, as assessed by an audiologist. 'Ventriculitis' was diagnosed by intraventricular paracentesis (in the first years of the study) and later by intraventricular ultrasound and computed tomography of the head. 'Hydrocephalus' was defined as an abnormal increase in head circumference or dilation of the ventricular system as detected by imaging studies. 'Seizure disorder' was defined as any convulsive disorder of any type that did not exist before the onset of meningitis and was present during and after hospitalization.

### 2.3. Data analysis

Data were analyzed using Epi-Info (version 3.5.3, CDC, Atlanta) and SPSS 19.0 (IBM SPSS Inc., USA). For the univariate analysis, the Chi-square test or Fisher's exact test was used to explore the association between treatment risk factors and sequelae; the relative risk (RR) and the 95% confidence interval (95% CI) were also calculated.

For the multivariate analysis, multinomial (polytomous) logistic regression analysis was used to evaluate whether treatment as a risk factor differed across sequelae, controlling for other risk factors. The multinomial logistic regression model was constructed comparing risks among each of the sequelae (hydrocephalus, seizure disorder, severe hearing loss, and ventriculitis) with no sequelae. Sequelae were used as dependent variables and all of the risk factors were included in the model as independent variables. Other important prognostic factors such as etiology (pneumococcal meningitis, meningococcal meningitis), age below 6 months, time period, and the interactions between steroids, type of pathogen, and type of antibiotic were also included in the multinomial logistic model to explore the independent association of antibiotics with neurologic sequelae. Odds ratios (ORs) and the 95% CI were calculated for the independent variables. To test the adequacy of the model a goodness-of-fit test was used. In univariate analysis, due to multiple comparisons, a $p$-value less than 0.01 was considered statistically significant, whilst in multivariate analysis a $p$-value less than 0.05 was considered statistically significant.

## 3. Results

In total, 2477 bacterial meningitis cases were recorded over the 32 years. The causative organisms most commonly included *Neisseria meningitidis*, Hib, and *Streptococcus pneumoniae*, with mean annual incidence rates of 8.9, 1.7, and 1.3 cases per 100 000 population, respectively. During the same period 2.2% (55/2477) of patients were confirmed with bacterial meningitis due to other pathogens (*Streptococcus spp*, *Staphylococcus spp*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus spp*, *Salmonella spp*, *Pseudomonas aeruginosa*, *Brucella melitensis*, Acinetobacter, *Enterobacter cloacae*, *Mycoplasma pneumoniae*, and *Rickettsia spp*), while 29.6% (732/2477) of bacterial meningitis cases were of unknown pathogen. The median age of those patients was 2.0 years with an interquartile range (IQR) of 0.5–5.0, and 58.7% were male. The median duration of symptoms before hospital admission was 24 h (IQR 24–48 h). The majority of patients presented with fever (1158/1242, 93.2%), meningeal signs (1212/1477, 82.1%), vomiting (1193/2074, 57.5%), and headache (871/1112, 78.3%). Less common manifestations included hemorrhagic rash (967/2466, 39.2%), bulging fontanel (416/918, 45.3%), and seizures (337/1777, 19.0%). The median CSF white cell count was $1468 \times 10^6$ cells/l, median CSF glucose was 42.0 mg/dl, and median CSF protein was 90.0 mg/dl. More detailed clinical and laboratory characteristics of the study population can be found in previous publications.[13–15] The estimated case fatality rate (CFR) from all causes was 3.8% (95/2477, 95% CI 3.1–4.7).

The rate of sequelae among survivors was estimated to be 3.3% (83 episodes occurred in 73/2207 patients, 95% CI 2.6–4.2). The morbidity rate was increased during the period 1993–1996 and the years 2003 and 2005 (Figure 1). Severe hearing loss was detected in only 1.0% of patients (23/2235 patients, 95% CI 0.7–1.6), ventriculitis in 1.0% of patients (22/2243 patients, 95% CI 0.6–1.5), hydrocephalus in 0.5% of patients (12/2243, 95% CI 0.3–1.0), and a seizure disorder was diagnosed in 1.1% of patients (24/2247, 95% CI 0.7–1.6).

The in-hospital treatment of patients who survived bacterial meningitis included ampicillin (1350 patients), penicillin (1102 patients), chloramphenicol (1353 patients), gentamicin (192 patients), and cephalosporins (265 patients). About seventy-one percent (70.9%) of patients received a combination of antibiotics. The most popular combination was penicillin with chloramphenicol (42.5%), followed by ampicillin with chloramphenicol (25.2%),

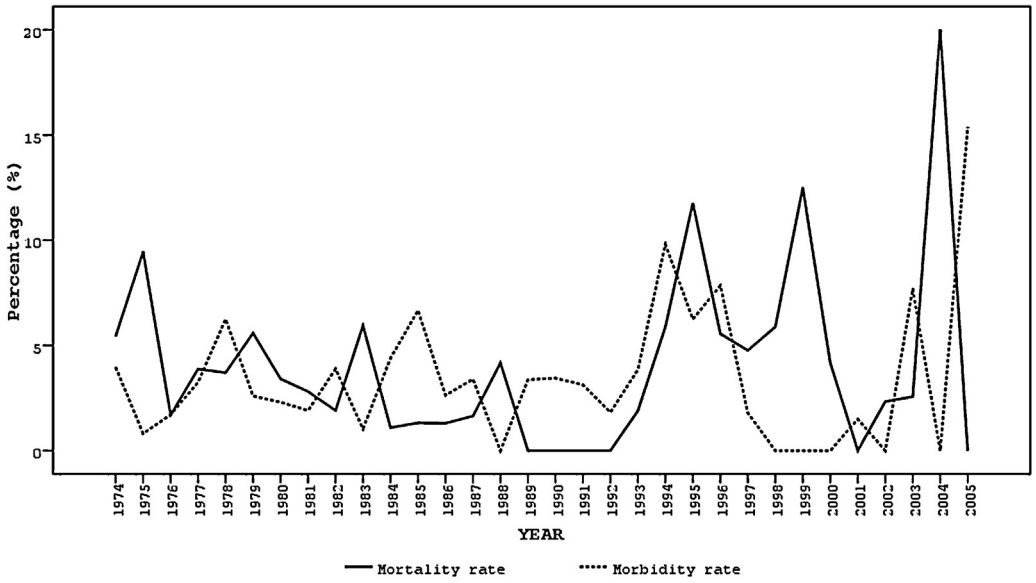


**Figure 1.** Mortality and morbidity rates over the 32-year study period (1974–2005).

ampicillin with gentamicin (only 7.2%), and penicillin with gentamicin (2.8%). Combinations with gentamicin were mainly used in the first period of the study, while those with chloramphenicol were popular choices in periods A and B. Figure 2 displays the use of ampicillin, penicillin, chloramphenicol, and cephalosporins over the 32-year study period. As shown in Figure 2, penicillin consumption increased from 1980 and it was used systematically until 2004, while a gradual replacement by cephalosporins started in 1998.

Adjuvant corticosteroids were administered to 1602 children (67.3%) overall, dexamethasone being the most commonly used corticosteroid (administered to 69.4% of corticosteroid recipients). Figure 3 shows the use of dexamethasone and hydrocortisone during the study period. Dexamethasone use was decreased during the period 1984–1987, while hydrocortisone use was increased during that period.

The results of the univariate analysis concerning therapeutic predictors of sequelae are presented in Table 1. According to this analysis the use of gentamicin was associated with seizure disorder (RR 5.66, 95% CI 2.43–13.17), with ventriculitis (RR 9.74, 95% CI 4.19–22.63), and with hydrocephalus (RR 5.39, 95% CI 1.64–17.72). Trimethoprim/sulfamethoxazole was associated with an elevated risk of ventriculitis (RR 10.21, 95% CI 4.40–23.72), seizures (RR 3.99, 95% CI 1.60–10.00), and hydrocephalus (RR 5.68, 95% CI 1.73–18.70). Chloramphenicol administration was found to be related to the development of seizures (RR 4.48, 95% CI 1.33–15.02). No other associations were identified between the other antibiotics and sequelae.

Since pneumococcal meningitis is more frequently associated with sequelae, the above analysis was also conducted selecting only the pneumococcal meningitis cases. The results found were similar to those of the previous analysis: gentamicin was associated with seizure disorder (RR 7.45, 95% CI 2.56–21.68) and with hydrocephalus (RR 10.21, 95% CI 1.56–67.04).

Additionally a univariate analysis was conducted exploring the association between corticosteroids and any of the sequelae in each pathogen category. It was observed that in cases of pneumococcal meningitis, dexamethasone was associated with a lower risk of hydrocephalus, seizure disorder, and severe hearing loss, but without statistical significance. In contrast, hydrocortisone


**Figure 2.** Antibiotic use over the 32-year study period (1974–2005).

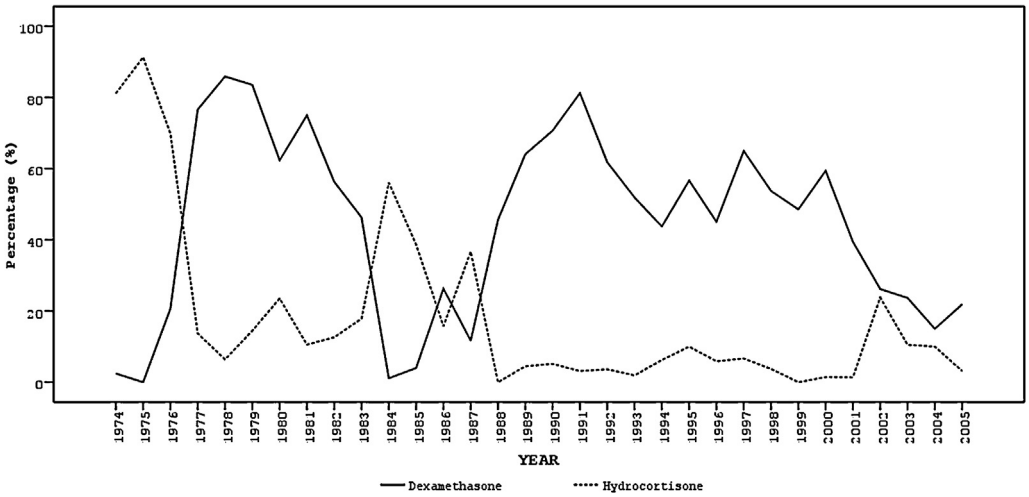


**Figure 3.** Dexamethasone and hydrocortisone use over the 32-year study period (1974–2005).

was associated with an increased risk of all of the sequelae subtypes, without statistical significance as well.

The results of the polytomous models are presented in Table 2. An elevated risk of seizure disorder (OR 4.72, 95% CI 1.12–19.96) and ventriculitis (OR 17.77, 95% CI 4.36–72.41) was found among the patients who received chloramphenicol. The use of cephalosporins was associated with an elevated risk of hydrocephalus (OR 5.24, 95% CI 1.05–26.29) and ventriculitis (OR 5.72, 95% CI 1.27–25.76). Trimethoprim/sulfamethoxazole was associated with an increased risk of hydrocephalus (OR 6.79, 95% CI 1.74–26.43), seizure disorder (OR 3.26, 95% CI 1.08–9.84), and ventriculitis (OR 8.60, 95% CI 2.97–24.91). Penicillin was associated with a lower risk of ventriculitis (OR 0.17, 95% CI 0.05–0.60). Ampicillin neither proved to be protective nor increased the risk of the development of any sequelae. Hydrocortisone was associated with a significant rise in hydrocephalus (OR 5.44, 95% CI 1.26–23.45). On the other hand, the protective effect of dexamethasone for hydrocephalus (OR 0.82, 95% CI 0.18–3.79) was not statistically significant.

According to the multinomial logistic regression analysis, pneumococcal meningitis was an independent risk factor for the development of seizure disorder (OR 10.47, 95% CI 3.24–33.82), as well as age below 6 months (OR 20.20, 95% CI 5.55–73.55). Moreover, bacterial meningitis in infancy was independently related to an increased risk of hydrocephalus (OR 7.40, 95% CI 1.75–31.37). Still, the risk of severe hearing loss was decreased in cases of meningococcal meningitis (OR 0.21, 95% CI 0.06–0.71) in comparison to other pathogens.

Finally, no significant interactions were identified between steroids, type of pathogen, and type of antibiotic for the risk of neurologic sequelae.

## 4. Discussion

Antibiotic treatment for childhood bacterial meningitis, including third-generation cephalosporins, as well as conventional antibiotics such as penicillin and chloramphenicol, has been proven generally safe and effective.[16,17] Nevertheless the use of adjuvant corticosteroids is still debated. The patient groups that are going to gain from their use need to be clearly identified, balancing benefits vs. disadvantages.[18,19]

The current study explored the association of treatment for childhood bacterial meningitis with the development of short-term sequelae using data from a large series of patients over an extended time-period. It is the first time that antibiotics used for the treatment of bacterial meningitis have been compared with regard to neurologic sequelae using a multinomial logistic regression model including other important parameters (pathogen, age of the patient, time period, etc.). According to our findings patients treated with chloramphenicol had an elevated risk of seizure disorder and ventriculitis. Chloramphenicol inhibits protein synthesis in bacteria and acts as a bacteriostatic drug for most pathogens, although it may be bactericidal to certain species such as *N. meningitidis, S. pneumoniae*, and Hib. It readily reaches therapeutic concentrations in the CSF, where values are approximately 60% of those in plasma,[20] and it tends to accumulate in brain tissue.[21] Occasionally results with chloramphenicol used for pneumococcal meningitis are unsatisfactory, because some strains are inhibited but not killed. Moreover, its administration has been implicated in the development of encephalopathy[22] and bilateral optic neuritis.[23] A possible explanation for the neurotoxicity of chloramphenicol may be either treatment failure or toxic accumulation of the drug in brain tissue.

Another drug that is no longer used for bacterial meningitis – trimethoprim/sulfamethoxazole – was found to increase the probability of hydrocephalus, seizures, and ventriculitis. It acts through inhibition of folic acid synthesis and causes bacteriostasis. The drug readily enters the CSF, and unfortunately the margin between toxicity for bacteria and humans is narrow. It has been reported to be associated with encephalopathy, psychosis, hallucinations, and aseptic meningitis, although the exact mechanism is unknown.[24,25]

Interestingly in our study, third-generation cephalosporins were related to an increased risk of hydrocephalus and ventriculitis. They act through the inhibition of cell wall synthesis and their effect is bactericidal. In a Cochrane review[16] of randomized controlled trials (RCTs), the effectiveness and safety of ceftriaxone or cefotaxime were compared with conventional treatment with penicillin or ampicillin–chloramphenicol in patients with community-acquired acute bacterial meningitis. No clinically important difference between ceftriaxone or cefotaxime and conventional antibiotics was identified. Concerning poor outcomes, the review shows a statistically significant increase only in the risk of diarrhea between the groups with the third-generation cephalosporins. On the other hand, evidence is accumulating that the administration of cephalosporins is related to neurotoxicity.[26] Clinical presentations can range from encephalopathy to non-convulsive status epilepticus.[27] Previous CNS disease, renal impairment, excess dosage of medication, and young age decrease the threshold for

**Table 1**
Sequelae in childhood bacterial meningitis according to treatment–univariate analysis

| Treatment | | Sequelae subtypes | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Hydrocephalus | | | | Seizure disorder | | | | Severe hearing loss | | | | Ventriculitis | | | |
| | | Count | % | RR (95% CI) | *p*-Value | Count | % | RR (95% CI) | *p*-Value | Count | % | RR (95% CI) | *p*-Value | Count | % | RR (95% CI) | *p*-Value |
| Ampicillin | Yes | 5/1328 | 0.4 | 0.47 (0.15–1.48) | 0.152 | 10/1330 | 0.8 | 0.51 (0.22–1.15) | 0.097 | 14/1327 | 1.1 | 1.12 (0.47–2.67) | 0.791 | 16/1329 | 1.2 | 2.1 (0.77–5.72) | 0.136 |
| | No | 7/874 | 0.8 | | | 13/875 | 1.5 | | | 8/852 | 0.9 | | | 5/873 | 0.6 | | |
| Penicillin | Yes | 9/1081 | 0.8 | 3.11 (0.84–11.46) | 0.072 | 16/1082 | 1.5 | 2.37 (0.98–5.74) | 0.048 | 8/1073 | 0.7 | 0.59 (0.25–1.40) | 0.225 | 6/1079 | 0.6 | 0.42 (0.16–1.16) | 0.060 |
| | No | 3/1121 | 0.3 | | | 7/1123 | 0.6 | | | 14/1106 | 1.3 | | | 15/1123 | 1.3 | | |
| Cephalosporins | Yes | 3/214 | 1.4 | 3.10 (0.85–11.35) | 0.103 | 4/214 | 1.9 | 1.96 (0.67–5.70) | 0.178 | 4/196 | 2.0 | 2.25 (0.77–6.58) | 0.129 | 4/214 | 1.9 | 2.19 (0.74–6.44) | 0.140 |
| | No | 9/1988 | 0.5 | | | 19/1991 | 1.0 | | | 18/1983 | 0.9 | | | 17/1988 | 0.9 | | |
| Gentamicin | Yes | 4/187 | 2.1 | 5.39 (1.64–17.72) | 0.014 | 8/190 | 4.2 | 5.66 (2.43–13.17) | <0.001 | 2/189 | 1.1 | 1.05 (0.25–4.47) | 0.581 | 10/188 | 5.3 | 9.74 (4.19–22.63) | <0.001 |
| | No | 8/2015 | 0.4 | | | 15/2015 | 0.7 | | | 20/1190 | 1.0 | | | 11/2014 | 0.5 | | |
| TMP/SMX | Yes | 4/178 | 2.2 | 5.68 (1.73–18.70) | 0.012 | 6/179 | 3.4 | 3.99 (1.60–10.00) | 0.008 | 2/180 | 1.1 | 1.11 (0.26–4.71) | 0.554 | 10/180 | 5.6 | 10.21 (4.40–23.72) | <0.001 |
| | No | 8/2024 | 0.4 | | | 17/2026 | 0.8 | | | 20/1999 | 1.0 | | | 11/2022 | 0.5 | | |
| Chloramphenicol | Yes | 11/1316 | 0.8 | 7.41 (0.96–57.26) | 0.019 | 20/1319 | 1.5 | 4.48 (1.33–15.02) | 0.008 | 15/1310 | 1.1 | 1.42 (0.58–3.47) | 0.438 | 17/1316 | 1.3 | 2.86 (0.97–8.47) | 0.047 |
| | No | 1/886 | 0.1 | | | 3/886 | 0.3 | | | 7/869 | 0.8 | | | 4/886 | 0.5 | | |
| Hydrocortisone | Yes | 7/539 | 1.3 | 4.43 (1.41–13.89) | 0.011 | 9/543 | 1.7 | 1.88 (0.83–4.28) | 0.125 | 4/538 | 0.7 | 0.66 (0.23–1.94) | 0.451 | 7/541 | 1.3 | 1.47 (0.60–3.58) | 0.396 |
| | No | 5/1704 | 0.3 | | | 15/1704 | 0.9 | | | 19/1967 | 1.1 | | | 15/1702 | 0.9 | | |
| Dexamethasone | Yes | 3/1088 | 0.3 | 0.35 (0.10–1.30) | 0.102 | 9/1087 | 0.8 | 0.64 (0.28–1.46) | 0.284 | 12/1086 | 1.1 | 1.15 (0.51–2.60) | 0.730 | 11/1087 | 1.0 | 1.06 (0.46–2.44) | 0.885 |
| | No | 9/1155 | 0.8 | | | 15/1160 | 1.3 | | | 11/1149 | 1.0 | | | 11/1156 | 1.0 | | |
| Steroids[a] | Yes | 8/1562 | 0.5 | 0.87 (0.26–2.89) | 0.519 | 18/1565 | 1.2 | 1.31 (0.52–3.28) | 0.566 | 16/1559 | 1.0 | 0.99 (0.41–2.40) | 0.984 | 17/1563 | 1.1 | 1.48 (0.55–3.99) | 0.436 |
| | No | 4/681 | 0.6 | | | 6/682 | 0.9 | | | 7/676 | 1.0 | | | 5/680 | 0.7 | | |

RR, risk ratio; CI, confidence interval; TMP/SMX, trimethoprim/sulfamethoxazole.
[a] Steroids: hydrocortisone and/or dexamethasone.

nervous toxicity. Animal studies suggest that the concentrations of antibiotic in the brain tissue rather than the concentrations in CSF are predictive of neurotoxicity.[28] One possible mechanism of action is provided through electrophysiological data. They suggest a direct antagonistic action of cephalosporins on the $GABA_A$ receptor complex, responsible for their epileptogenic effects, similar to other beta-lactam antibiotics.[29] However, the precise pathophysiology remains poorly understood.

It was found in the current study that the use of penicillin did not increase the risk of any sequelae, and it was also found protective for ventriculitis. A possible explanation of this finding could be related to the superior bioavailability of the drug in the course of CNS inflammation. This finding underlines the importance of an all-time classic and low cost antibiotic, which is still the first choice for sensitive strains of meningococci and pneumococci. Interestingly the epileptogenic effect of penicillin through inhibition of $GABA_A$ receptors[28] was not shown in our series.

Hydrocortisone was associated with a rise in hydrocephalus. This finding may be attributed to the fact that historically hydrocortisone was administered to severely compromised patients on admission. The use of hydrocortisone for bacterial meningitis was studied in the early seventies,[30,31] but it was soon replaced with dexamethasone, which proved to have a more potent anti-inflammatory effect. In our study, dexamethasone was not found to be protective for the development of hearing loss, but we had some indications of a protective effect for the development of hydrocephalus, without statistical significance. In 1988 Lebel et al., in a placebo-controlled study, were the first to show a beneficial effect of dexamethasone on hearing impairment in childhood bacterial meningitis.[32] Since then multiple clinical and experimental studies have tried to clarify this issue.[33–37] According to a Cochrane review,[18] corticosteroids prevent hearing loss in children with bacterial meningitis (RR 0.74, 95% CI 0.62–0.89), especially children with meningitis caused by *H. influenzae* type b (RR 0.34, 95% CI 0.20–0.59) and children in high-income countries (RR 0.67, 95% CI 0.46–0.97). A second meta-analysis that included five trials, published after 2001, concluded that dexamethasone did not affect mortality, as well as hearing loss or other neurologic sequelae.[38] The available evidence shows that dexamethasone use prevents hearing impairment in Hib meningitis only, whereas there is not enough evidence in favor of the systematic use of steroids in pneumococcal meningitis and no evidence for meningococcal cases.[12] Moreover, the risk of other neurological sequelae does not appear to be reduced in patients with bacterial meningitis who receive adjuvant corticosteroids.[18] We have to acknowledge that better conclusions could be achieved if we had data on the specific reason for the prescription of the corticosteroids.

Additional studies will be necessary after the introduction of newer pneumococcal conjugate vaccines, which are expected to significantly change the epidemiology of bacterial meningitis, especially in those areas where pneumococcal meningitis is the leading cause of acute bacterial meningitis. Some evidence already shows that invasive disease from vaccine serotypes is going to be severely decreased.[39] In this case the need for dexamethasone should be re-evaluated, while at the same time monitoring should be done for a shift to non-vaccine serotypes.

In conclusion, the current study findings provide some evidence that the type of antimicrobial treatment for childhood bacterial meningitis may influence the development of neurological sequelae. The use of penicillin was found to have a protective effect, while chloramphenicol, cephalosporins, and trimethoprim/sulfamethoxazole increased the risk of neurological sequelae. Concerning steroids, hydrocortisone increased the risk of hydrocephalus, while a protective effect of dexamethasone was not statistically significant. The current study findings in combination

**Table 2**
Multivariate analysis of treatment and other prognostic factors for sequelae in childhood bacterial meningitis[a]

| Treatment and other prognostic factors | Sequelae subtypes | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Hydrocephalus | | | Seizure disorder | | | Severe hearing loss | | | Ventriculitis | | |
| | OR | 95% CI | *p*-Value | OR | 95% CI | *p*-Value | OR | 95% CI | *p*-Value | OR | 95% CI | *p*-Value |
| Ampicillin | 0.44 | (0.10–1.92) | 0.276 | 0.65 | (0.20–2.09) | 0.472 | 0.63 | (0.17–2.39) | 0.498 | 0.64 | (0.16–2.46) | 0.512 |
| Penicillin | 1.19 | (0.23–6.17) | 0.838 | 1.01 | (0.29–3.57) | 0.989 | 0.40 | (0.11–1.55) | 0.186 | 0.17 | (0.05–0.60) | 0.006 |
| Cephalosporins | 5.24 | (1.05–26.29) | 0.044 | 1.49 | (0.34–6.54) | 0.599 | 1.47 | (0.38–5.60) | 0.577 | 5.72 | (1.27–25.76) | 0.023 |
| Gentamicin | 1.85 | (0.41–8.44) | 0.426 | 2.14 | (0.66–6.91) | 0.205 | 1.27 | (0.24–6.78) | 0.783 | 2.85 | (0.90–8.99) | 0.075 |
| TMP/SMX | 6.79 | (1.74–26.43) | 0.006 | 3.26 | (1.08–9.84) | 0.036 | 1.32 | (0.29–5.99) | 0.718 | 8.60 | (2.97–24.91) | <0.001 |
| Chloramphenicol | 7.62 | (0.79–73.92) | 0.080 | 4.72 | (1.12–19.96) | 0.035 | 1.31 | (0.39–4.42) | 0.664 | 17.77 | (4.36–72.41) | <0.001 |
| Dexamethasone | 0.82 | (0.18–3.79) | 0.796 | 1.21 | (0.41–3.55) | 0.729 | 1.22 | (0.49–2.99) | 0.670 | 2.31 | (0.71–7.53) | 0.166 |
| Hydrocortisone | 5.44 | (1.26–23.45) | 0.023 | 2.06 | (0.63–6.75) | 0.231 | 0.80 | (0.21–3.07) | 0.746 | 2.50 | (0.68–9.20) | 0.167 |
| *S. pneumoniae* | 3.27 | (0.77–13.90) | 0.108 | 10.47 | (3.24–33.82) | <0.001 | 1.42 | (0.36–5.60) | 0.612 | 2.17 | (0.47–9.92) | 0.319 |
| *N. meningitidis* | 0.33 | (0.06–1.81) | 0.200 | 1.35 | (0.41–4.52) | 0.623 | 0.21 | (0.06–0.71) | 0.012 | 0.54 | (0.16–1.83) | 0.322 |
| Age <6 months | 7.40 | (1.75–31.37) | 0.007 | 20.20 | (5.55–73.55) | <0.001 | 0.63 | (0.19–2.13) | 0.456 | 2.63 | (0.89–7.78) | 0.081 |
| Period A[b] | 0.61 | (0.14–2.62) | 0.511 | 0.75 | (0.24–2.32) | 0.620 | 0.50 | (0.15–1.65) | 0.258 | 3.09 | (0.75–12.72) | 0.118 |

OR, odds ratio; CI, confidence interval; TMP/SMX, trimethoprim/sulfamethoxazole.
[a] This analysis is based on 88.7% of the study population due to missing values. The adequacy of the model results was examined by the likelihood ratio Chi-square statistic, a goodness-of-fit test ($p = 0.999$).
[b] Period A: 1974–1984.

with those of other reports in the literature suggest a causative relationship between antimicrobial therapy and the outcome of bacterial meningitis. Future studies may further elucidate these findings.

## Acknowledgements

We would like to thank all of the pediatricians who participated in the collection of data by filling in the registry forms, as well as Ms Vlasserou Fotini and Ms Atsali Erato for their contribution in accumulating the data. Moreover, we would like to thank Prof. Syriopoulou Vasiliki, Ms Mostrou Glyceria, and honorary Assistant Professor Dimitrios Zoumboulakis for their long-standing invaluable contribution to the organization and realization of the Meningitis Registry. In addition, we highly appreciate the contribution of Dr J. Economides who performed the hearing screening of children with bacterial meningitis. There was no funding source.

*Ethical approval:* This study was approved by the ethics committee of Agia Sofia Children's Hospital. Patient consent was not required, since no personal data were included in this study.

*Conflict of interest:* No conflict of interest to declare.

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