

Penicillin and Ceftriaxone Susceptibility of *Streptococcus pneumoniae* Isolated from Cerebrospinal Fluid of Children with Meningitis Hospitalized in a Tertiary Hospital in Israel

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ABSTRACT: **Background:** *Streptococcus pneumoniae* is now the predominant pathogen causing meningitis. The resistance of *S. pneumoniae* to penicillin and third-generation cephalosporins has grown steadily.

Objectives: To assess the antibiotic susceptibility of *S. pneumoniae* isolated from the cerebrospinal fluid of children with meningitis, and determine the antibiotic regimen appropriate for suspected bacterial meningitis in Israel.

Methods: The study group included 31 children with 35 episodes of meningitis hospitalized from 1998 to 2006. *S. pneumoniae* isolates from the cerebrospinal fluid were tested for susceptibility to penicillin and ceftriaxone.

Results: Of the 35 isolates, 17 (48.6%) showed resistance to penicillin (minimum inhibitory concentration ≥ 0.12 $\mu\text{g/ml}$). Only 3 isolates (8.6%) showed intermediate resistance to ceftriaxone (≥ 0.5 and < 2 $\mu\text{g/ml}$), and none showed complete resistance (MIC ≥ 2 $\mu\text{g/ml}$). The rates of antibiotic resistance were higher in children who were treated with antibiotics prior to admission (penicillin 88.9% vs. 34.6%, $P = 0.007$; ceftriaxone 22.2% vs. 3.8%, $P = 0.156$).

Conclusions: The rate of penicillin resistance is high in children with *S. pneumoniae* meningitis in Israel, especially in those treated with oral antibiotics prior to admission. Resistance to ceftriaxone is infrequent though not negligible. On the basis of these findings, current recommendations to empirically treat all children with suspected bacterial meningitis with ceftriaxone in addition to vancomycin until the bacterial susceptibility results become available are justified also in Israel.

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KEY WORDS: ceftriaxone, cerebrospinal fluid, meningitis, *Streptococcus pneumoniae*, susceptibility

The introduction of widespread vaccination against *Hemophilus influenzae* type B infection changed the epidemiology of bacterial meningitis. *Streptococcus pneumoniae* is now the predominant pathogen in children aged one month or more, followed by *Neisseria meningitidis* in areas where the administration of the heptavalent conjugated pneumococcal vaccine is not routinely administered [1,2].

S. pneumoniae meningitis is associated with substantial rates of morbidity (20–30%) and mortality (10%), which have hardly improved in the past 30 years despite effective antimicrobial therapy [3]. The resistance of *S. pneumoniae* to penicillin and third-generation cephalosporins has grown steadily since the isolation of the first penicillin-resistant strain in 1967. The prevalence rate of *S. pneumoniae* resistance varies substantially among and within countries [4–11].

The decrease in the frequency of *H. influenzae* meningitis and the increase in pneumococcal antimicrobial resistance have affected the empirical management of meningitis [1,12]. Broad-spectrum cephalosporins (cefotaxime and ceftriaxone) were used as standard therapy in infants and children in the mid-1980s [1,10,13]. However, in the mid-1990s, reports of cephalosporin-resistant pneumococcal meningitis [8,14] prompted the Committee on Infectious Diseases and most experts in the United States to recommend adding vancomycin for empiric therapy in suspected cases [15].

In Israel, the susceptibility of *S. pneumoniae* from cerebrospinal fluid has not yet been studied. The management of bacterial meningitis is presently based on prevalence rates of *S. pneumoniae* resistance associated with other invasive diseases and other geographic regions. Improved knowledge of the regional susceptibility distribution of *S. pneumoniae* isolated from the CSF of children with meningitis would help confirm the current practice in Israel based on *S. pneumoniae* susceptibility from non-meningeal infection in Israel, foreign literature and guidelines from the United States.

MIC = minimum inhibitory concentration

CSF = cerebrospinal fluid

PATIENTS AND METHODS

The study was conducted at Schneider Children's Medical Center of Israel, an urban pediatric tertiary-care center that handles approximately 52,000 emergency room visits per year. A retrospective design was used. The study group comprised all children (aged 0–18 years) hospitalized in our institute for pneumococcal meningitis throughout 9 years: January 1998 to December 2006. The diagnosis of pneumococcal meningitis was based on the finding of a positive CSF culture. Patients were identified by active surveillance of all microbiology laboratory records. In all cases, a standardized case report form was completed, specifying the history, physical examination findings, laboratory data, hospital course, treatment, culture growth and pneumococci susceptibilities. Prior antibiotic treatment was defined as antibacterial medication administered within 7 days before admission. The study was conducted in the pre-conjugated heptavalent vaccine era.

Susceptibility to antibiotic therapy was evaluated according to the new guidelines of the Clinical and Laboratory Standards Institute (CLSI) published in January 2008. Isolates from patients with meningitis are now categorized as either susceptible or resistant, with intravenous penicillin breakpoints of ≤ 0.06 or ≥ 0.12 $\mu\text{g/ml}$, respectively. Because the blood-brain barrier limits penetration of penicillin into the cerebrospinal fluid, no intermediate category for meningitis exists. Susceptible, intermediate, and resistant minimum inhibitory concentration breakpoints for ceftriaxone were ≤ 0.5 , 0.5 – 2 , and ≥ 2 $\mu\text{g/ml}$, respectively [16]. The study was approved by the local institutional ethics review board.

STATISTICAL ANALYSIS

Patients were divided according to continuous and categorical variables and compared for antibiotic resistance by analysis of variance (ANOVA) and two-tailed Fisher's exact test, respectively. A *P* value of 0.05 or lower was considered statistically significant.

RESULTS

The study group consisted of 31 children with culture-positive pneumococcal meningitis. Their demographic and clinical characteristics are shown in Table 1. Two children had more than one episode of the disease (total, 35 episodes). Four children had an underlying condition that may have predisposed them to bacterial meningitis.

HOSPITAL COURSE

The mean hospitalization duration was 14 days, median 13 days. Seventeen children (49%) were hospitalized in the intensive care unit; 13 of them were transferred directly from

Table 1. Clinical and demographic characteristics at admission of 31 patients with 35 episodes of pneumococcal meningitis

Characteristics	Value
Median age (mos) (range)	16 (1.5–174)
Gender	
Males	22 (63%)
Females	13 (37%)
Ethnic group	
Jews	30 (86%)
Arabs	5 (14%)
Pretreatment with antibiotics	9 (27%)
Previously hospitalized	13 (37%)
Seizures before admission	14 (40%)
Underlying conditions	
Asplenia*	3
Congenital heart disease**	2
Liver transplant recipient	1
Hydrocephalus and suspected immunodeficiency***	1

*Children with asplenia included a 14.5 year old boy with relapse of Hodgkin lymphoma and splenectomy, a 6.5 year old boy with congenital hyposplenia and a previous episode of pneumococcal pneumonia, and a 2 year old infant with congenital asplenia, right isomerism and complete atriovenous canal.

**Both children with congenital heart disease had an atriovenous canal; one of them also had asplenia.

***One 18 month old girl had *Escherichia coli* meningitis with consequent hydrocephalus, treated by placement of a ventriculo-atrial shunt, which was followed by *Pseudomonas* shunt infection and two episodes of pneumococcal meningitis.

Note: All values are n or n (%) unless otherwise specified.

the emergency room and 4 were transferred from the ward due to deterioration in their condition. The duration of fever in hospital (after treatment) ranged from 1 to 7 days, mean 2.3 days and median 2 days. All children were treated with ceftriaxone, and all but two also received vancomycin; 21 patients (60%) were treated with steroids.

OUTCOME

One patient died in hospital, and another died a few months later from a relapse of lymphoma. Of the remainder, 13 children had long-term impairments ranging from mild hearing loss to severe brain damage, 11 had no sequelae and 6 patients were lost to follow-up.

ANTIBIOTIC SUSCEPTIBILITY

With regard to penicillin 51.4% were susceptible (N=18) and 48.6% resistant (N=17), for ceftriaxone 91.5% were susceptible (N=32), 8.5% intermediate (N=3) and none resistant.

The rate of resistance to penicillin was significantly higher in children who received oral antibiotic treatment prior to admission than in children who did not (88.9% vs. 34.6%, *P* = 0.007). The penicillin resistance rate was also higher in children with prior hospitalization than in non-hospitalized children, but the difference was not statistically significant (61.5% vs. 40.9%, *P* = 0.305).

The rate of resistance to ceftriaxone was higher (though not significantly) in the children who received prior oral antibiotic treatment than in the children who did not (22.2% vs. 3.8%, $P = 0.156$). The rate of ceftriaxone resistance was not different between children with prior hospitalization than in the non-hospitalized (9% vs. 7.7%, $P = NS$).

DISCUSSION

Suspected bacterial meningitis will continue to be treated empirically until more rapid susceptibility testing and pathogen-identification techniques become available. Following the emergence of pneumococcal resistance to cephalosporin [15], the American Academy of Pediatrics recommended that vancomycin be included in the empiric therapy of bacterial meningitis. However, the role of vancomycin therapy in this setting is not well established outside the U.S., and particularly in Israel [17]. Furthermore, vancomycin was initially considered suboptimal therapy for bacterial meningitis because achievable CSF levels are modest [18].

Surveillance studies of the antibiotic susceptibility of *S. pneumoniae* have been carried out nationwide in many countries [4-11]. Based on the former susceptibility definitions, in Japan, which reported the highest resistance rate, the prevalence of strains fully resistant to penicillin and partially resistant to ceftriaxone is currently 45.2% [11].

In Israel, the antibiotic resistance of *S. pneumoniae* in children with invasive infection is still evolving. Rates of penicillin resistance rose from 18% in 1987-1993 [19,20] to 22% in 1989-98 [21], and up to 35% in 1998-99 [22]. Rates of ceftriaxone resistance rose from zero in 1987-93 to 10% intermediate resistance in 1998-99 [22]. Failure of cefotaxime treatment for penicillin-resistant *S. pneumoniae* meningitis was reported once, in 1997 [23]. The trend of antibiotic resistance was also reported in Israel regarding other pathogens [24].

In the present study, 17 of the 35 CSF isolates tested (48.6%) were penicillin-resistant pneumococci. Three isolates (8.6%) showed intermediate resistance to ceftriaxone. The rate found here for penicillin resistance was higher than reported to date in Israel, partially due to changing definitions of susceptibility. The trend of increasing prevalence of pneumococcal resistance to antibiotics is in line with findings in other countries [5,25]. Studies have shown that therapeutic failures may occur when ceftriaxone is used to treat disease caused by strains resistant to these antibiotics (MIC ≥ 2 mg/ml), in our study no such case was presented. When the MIC is 1.0 mg/ml for cefotaxime or ceftriaxone (intermediate resistance), the response is unpredictable [25]. Given our results of a high rate of penicillin-resistant strains and a non-negligible rate for ceftriaxone-nonsusceptible strains, we suggest that in Israel, like in the U.S. and Europe, the combination of vancomycin and ceftriaxone should remain

the preferred empiric therapy for suspected pneumococcal meningitis.

We found a higher resistance rate among children who were previously hospitalized (61.5% to penicillin and 7.7% to ceftriaxone), and an even higher rate among children who were treated with antibiotics prior to admission (88.9% to penicillin and 22.2% to ceftriaxone). However, owing to the relatively small size of our sample, the statistical power was insufficient to detect significant differences between the groups. Nevertheless, these results further emphasize the importance of the judicious administration of antibiotics in the hospital and in the community.

Continued monitoring of resistance characteristics is necessary in pneumococcal isolates from the CSF of hospitalized children in Israel. Moreover, the long-term solution is prevention of antimicrobial-resistant infections by the heedful use of antimicrobials combined with routine administration of the newly available heptavalent conjugate vaccine against *S. pneumoniae*, which is now given as a routine vaccination in Israel. It would be of considerable interest to study the influence of the routine vaccination on the penicillin non-susceptible *S. pneumoniae* over the years.

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