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The Causative Organisms of Bacterial Meningitis in Korean Children in 1996-2005

Bacterial meningitis remains a serious cause of morbidity and mortality in childhood, despite the availability of effective vaccines against *Haemophilus influenzae* type b (Hib) or *Streptococcus pneumoniae*. The purpose of this study was to analyze data on bacterial meningitis cases in Korea from 1996 through 2005. The information of all hospitalized bacteria-proven meningitis cases was obtained from 17 university hospitals nationwide. A total of 402 cases were identified. Of these, 125 (29.9%) cases were neonates. *Streptococcus agalactiae* was the most common bacteria responsible for 99 (24.6%) of all cases regardless of age, followed by *S. pneumoniae* for 91 (22.6%) and *H. influenzae* for 67 (16.7%) patients. The common etiology beyond the neonatal period was *S. pneumoniae* for 91 (33.0%) followed by *H. influenzae* for 63 (22.8%) patients. The overall case fatality rate was 9.4%, which was similar with that in 1986-1995. In conclusion, *S. agalactiae*, *S. pneumoniae* and *H. influenzae* were important etiologic agents of bacterial meningitis in children in the last 10 yrs. It is required to establish the preventive strategy of the three bacteria. The nationwide epidemiologic study should be continued to evaluate immunization strategy and efficacy.

Key Words : *Meningitis, Bacterial; Etiology; Epidemiology; Streptococcus pneumoniae; Haemophilus influenzae; Streptococcus agalactiae; Neisseria meningitidis*

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INTRODUCTION

Despite increased availability of potent antimicrobials and effective vaccines, bacterial meningitis continues to be a significant cause of childhood morbidity and mortality. Many clinical and etiologic studies performed over the past decades have demonstrated that different species of bacteria cause purulent meningitis. In neonatal period, *Streptococcus agalactiae* and Gram-negative bacilli cause most bacterial meningitis (1, 2). *Haemophilus influenzae*, *Neisseria meningitidis* and *Streptococcus pneumoniae* were the most common causative organisms of bacterial meningitis worldwide in childhood (3, 4). In Korea, there was a report representing the basic epidemiologic data of bacterial meningitis in children during the previous ten years (1986-1995) (5). Thereafter, new vaccines such as *Haemophilus influenza* type b (Hib) conjugate vaccine and heptavalent pneumococcal conjugate vaccine have been introduced and many changes of the epidemiologic profile are expected in Korea. Particularly, Hib vaccine was proved to have good immunogenicity in Korean infants (6). Although decline of invasive Hib diseases including meningitis has been reported in many countries after the routine immunization of Hib vaccine (7, 8), there is little investigation about childhood bacterial meningitis in Korea. Some studies demonstrated that the incidence of Hib meningitis had decreased after the introduction of Hib vaccine (9, 10). However, as

these studies were carried out in only one hospital or several hospitals in a specific region, they might be insufficient to reflect the general pediatric population in Korea.

This study provides the comprehensive data of bacterial meningitis in Korean children through a multicenter retrospective study for the past decade. Also, it will provide invaluable data for comparison of clinical features of the disease in 1986-1995 with those in 1996-2005.

MATERIALS AND METHODS

Data on the medical records of bacterial meningitis patients aged ≤18 yr admitted to 17 university hospitals throughout Korea from January 1996 through December 2005, were reviewed retrospectively. Among the hospitals participated in this study, six were located in Seoul, another six in cities nearby Seoul, and each of five hospitals was located in Gangwon-do (Wonju), Chungcheongnam-do (Cheonan), Jeollabuk-do (Jeonju), Gwangju, and Busan, respective. All bacteria isolated in the patients with meningitis were included. *Staphylococcus epidermidis* cultured in patients with cerebrospinal shunts were excluded from the analysis. In this study, the criteria for a definite diagnosis of bacterial meningitis were as following: 1) positive cerebrospinal fluid (CSF) culture of bacterial pathogen; 2) positive blood culture of bacteria with clinical features and CSF findings concordant with bacterial meningitis; and 3) CSF positive for organisms causing bacterial meningitis by latex agglutinin test and with pleocytosis (≥10 cells/μL) in patients with meningeal irritative signs. Medical records were examined for the followings: age, gender, bacterial etiology of meningitis, fatality and complications. Organisms were identified according to standard procedures in each hospital, but bacterial isolates were not subcultured or serotyped.

RESULTS

During the ten years, 402 patients were hospitalized with bacterial meningitis in 17 hospitals. Of these, 231 patients (57.5%) were male, and 169 patients (42.0%) were female with a male to female ratio of 1.37:1. The ages of infected children ranged from 0 day to 18 yr with a mean and median age of 25 months and 3 months, respectively. Most patients (330 cases, 82.1%) were ≤2 yr of age and 125 (31.2%) cases were neonates.

S. agalactiae (99 cases, 24.6%) was the most frequent etiologic agent in Korea, followed by *S. pneumoniae* (91 cases, 22.6%) and *H. influenzae* (67 cases, 16.7%). And *Escherichia coli* (21 cases, 5.2%) and *N. meningitidis* (18 cases, 4.5%) were important pathogens of bacterial meningitis in Korean children. The category "others" included coagulase negative *Staphylococcus* (26 cases, 6.5%), *Streptococcus* (other than *S. agalactiae*) (15 cases, 3.7%), *Staphylococcus aureus* (15 cases, 3.7%), *Klebsiella pneumoniae* (11 cases, 2.7%), *Enterococcus* sp. (10 cases, 2.5%), *Enterobacter cloacae* (5 cases, 1.2%), *Salmonella* sp. (4 cases, 1.0%), *Acinetobacter* sp. (4 cases, 1.0%), *Listeria* sp. (3 cases, 0.7%), *Pseudomonas aeruginosa* (3 cases, 0.7%), *Mycobacterium tuberculosis*, *Proteus mirabilis*, *Flavobacterium indologans* and Gram-negative bacilli (Table 1).

In the first 3 months of life, *S. agalactiae* (89 of 187, 47.6%) and *E. coli* (18 of 187, 9.6%) were common organisms causing bacterial meningitis. Among *S. agalactiae* meningitis, only 8 cases presented within 6 days after birth and the remaining cases presented between 7 days and 5 months. The common etiology beyond the neonatal period and under 5 yr of age was *S. pneumoniae* for 32.1% (68 of 212), followed by *H. influenzae* for 27.8% (59 of 212). In patients between 5 and 18 yr, *S. pneumoniae* (23 of 64, 35.9%) and *N. meningitidis* (15 of 64, 23.4%) were the major etiologic organisms of bacterial meningitis.

Through the ten years, yearly frequency of bacterial meningitis was similar, however the cases of meningitis caused by *H. influenzae* have decreased during the period, especially since 2001 (Fig. 1). Among a total of 67 *H. influenzae* meningitis cases, 51 (76.1%) occurred between 1996 and 2000, thus, the number of cases decreased by a third between 2001 and 2005.

Overall mortality rate was 9.5%. The fatalities as etiolog-

Table 1. Age distribution of bacterial meningitis cases according to causative organisms, 1996-2005

Age of patient	No. (%) caused by						Total
	S. agalactiae	*E. coli*	*H. influenzae*	*S. pneumoniae*	*N. meningitidis*	Others	
0 month	59 (47.2)	10 (8.0)	4 (3.2)	0	2 (1.6)	50 (40.0)	125
1-2 month	30 (48.4)	8 (12.9)	7 (11.3)	3 (4.8)	0	14 (22.6)	62
3-59 month	9 (6.0)	3 (2.0)	52 (34.7)	65 (43.3)	1 (0.7)	20 (13.3)	150
5-18 yr	0	0	4 (6.3)	23 (35.9)	15 (23.4)	22 (34.4)	64
Total	98* (24.4)	21 (5.2)	67 (16.7)	91 (22.7)	18 (4.5)	106 (26.4)	401*

The category "others" included coagulase negative *Staphylococcus* (26 cases, 6.5%), *Streptococcus* (other than *S. agalactiae*) (15 cases, 3.7%), *Staphylococcus aureus* (15 cases, 3.7%), *Klebsiella pneumoniae* (11 cases, 2.7%), *Enterococcus* species (10 cases, 2.5%), *Enterobacter cloacae* (5 cases, 1.2%), *Salmonella* species (4 cases, 1.0%), *Acinetobacter* species (4 cases, 1.0%), *Listeria* species (3 cases, 0.7%), *Pseudomonas aeruginosa* (3 cases, 0.7%), *Mycobacterium tuberculosis*, *Proteus mirabilis*, *Flavobacterium indologans* and gram-negative bacilli.
*Age not determined: 1.

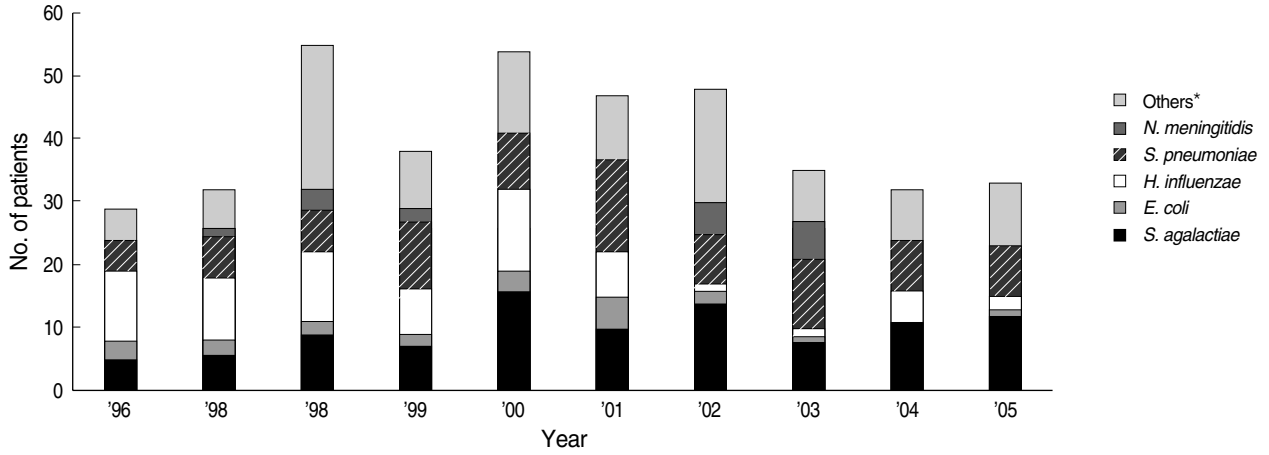

Fig. 1. Yearly distribution of bacterial meningitis according to etiologic agents. The incidence of *H. influenzae* meningitis has markedly decreased since 2001.
*The category "others" included coagulase negative *Staphylococcus* (26 cases, 6.5%), *Streptococcus* (other than *S. agalactiae*) (15 cases, 3.7%), *Staphylococcus aureus* (15 cases, 3.7%), *Klebsiella pneumoniae* (11 cases, 2.7%), *Enterococcus* species (10 cases, 2.5%), *Enterobacter cloacae* (5 cases, 1.2%), *Salmonella* species (4 cases, 1.0%), *Acinetobacter* species (4 cases, 1.0%), *Listeria* species (3 cases, 0.7%), *Pseudomonas aeruginosa* (3 cases, 0.7%), *Mycobacterium tuberculosis*, *Proteus mirabilis*, *Flavobacterium indologans* and Gram-negative bacilli.

Table 2. Case fatality according to causative organisms

Etiology	Case fatality rates No. of death/No. of patients (%)
S. agalactiae	8/99 (8.0)
E. coli	1/21 (4.8)
H. influenzae	0/67 (0.0)
S. pneumoniae	18/91 (19.8)
N. meningitidis	3/18 (16.7)
Others	8/106 (7.5)
Total	38/402 (9.5)

ic agents were 19.8%, 16.7% and 8.0% for *S. pneumoniae*, *N. meningitidis* and *S. agalactiae*, respectively (Table 2). There was no fatal case in meningitis patients caused by *H. influenzae*. Various complications were developed in 20.1% of patients; subdural effusion (7.5%), hydrocephalus (6.2%), hearing impairment (5.5%), convulsion (3.5%), etc. The incidences of complications according to etiologic agents were 27.3%, 26.9%, 23.8%, 20.9%, and 5.6% for *S. agalactiae*, *H. influenzae*, *E. coli*, *S. pneumoniae* and *N. meningitidis*, respectively.

DISCUSSION

This study provides the epidemiologic data about bacterial meningitis in Korean children during the last decade. We have shown the basic epidemiologic information of childhood bacterial meningitis in a previous study. Therefore, these studies reflect the epidemiologic trend of bacterial meningitis in Korean children for the last 20 yr. It cannot provide the incidence of bacterial meningitis in the general population of Korea, but can offer the relative frequency of causative organisms by a multicenter study including hospitals distributed throughout Korea. This investigation became more representative of population characteristics because hospitals located in more regions participated in it compared with the previous study.

From 1996 through 2005, the most common organism of bacterial meningitis in Korean children was *S. agalactiae*, followed by *S. pneumoniae* and *H. influenzae*. This result differs from the previous report that the leading causative organism of bacterial meningitis was *S. pneumoniae* (35.0%), followed by *H. influenzae* (34.3%) and *N. meningitidis* (6.4%) between 1986 and 1995 (5). However, the main reason of this difference is due to the fact that the subjects of this study included neonates. In many developed countries, *S. agalactiae* caused most bacterial meningitis in the neonatal period including premature and term babies up to 3 months of life (11, 12). The incidence of neonatal *S. agalactiae* infection has decreased since the implementation of intrapartum chemoprophylaxis in the United States and some European countries (13, 14). In the United States, Center for Disease Control and Prevention revised national guidelines in 2002, first issued in 1996, which recommended universal late antenatal screening of all pregnant women. However, the overall rates of late-onset disease remained stable in spite of these guidelines, that is, it has only influenced the incidence of early-onset *S. agalactiae* disease, not that of late-onset disease (1). In this study 8.1% of *S. agalactiae* meningitis patients presented within the first 6 days of life in contrast to the previous report 54.4% and 59.6% in the United States and European countries, respectively (1, 2). Considering the results of this study, intrapartum antibiotic prophylaxis might not have a great

impact in the reduction of *S. agalactiae* disease in Korea. Other preventive strategies of neonatal *S. agalactiae* infections such as vaccination against this pathogen might be required.

Beyond the neonatal period, *S. pneumoniae* and *H. influenzae* were major organisms causing bacterial meningitis during the study period. *H. influenzae* has decreased as a major pathogen of meningitis during ten years, especially since 2001 after Hib vaccine was introduced in Korea. Hib had been the highest portion of etiologic agents of childhood bacterial meningitis when Hib vaccine was not yet introduced (15). In many countries, after Hib vaccine was introduced in national immunization programs invasive infections caused by Hib reduced by more than 99% (3, 4, 16, 17). Replacement with other capsular types has not occurred after the introduction of Hib vaccines (18). In 2006, WHO recommended that Hib vaccines be included in all routine infant immunization programs (19). Although *H. influenzae* isolates were not routinely serotyped in this study, the reduced incidence of *H. influenzae* meningitis in Korea can be thought to be contributed by effectiveness of Hib vaccine because more than 95% of invasive diseases are caused by type b strain (3). Thus, with the universal administration of Hib vaccine, further reduction of the incidence of bacterial meningitis caused by *H. influenzae* may be expected in Korea.

S. pneumoniae is the most common etiology of childhood bacterial meningitis in the United States and Africa region, especially where Hib disease has been eliminated by vaccination (20-22). It is the second most frequently reported cause of septic meningitis in European and sub-Saharan African countries following meningococcal cases (23-25). Heptavalent pneumococcal conjugate vaccine (PCV7) covers against seven of the most common and resistant strains (4, 6B, 9V, 14, 18C, 19F, and 23F) of *S. pneumoniae*. The incidence of pneumococcal meningitis declined by 30.1%, especially nearly 60% in children younger than 5 yr of age after the introduction of conjugate vaccine against in the United States (26). However, despite the introduction of PCV7, *S. pneumoniae* remains the most common cause of childhood bacterial meningitis in the United States (20). The reason of this has been attributed to the replacement for pneumococcal meningitis is observed for non-vaccine serotypes after widespread use of PCV7, unlike *H. influenzae* (26). In addition, the circulating serotypes can vary with geographical areas and relatively high proportion of serotype 19A has been found among prevalent serotypes of Korea (27). Thus, 10-valent (including serotype 1, 5 and 7V) and 13-valent vaccine (including serotype 1, 3, 5, 6A, 7F, and 19A) were developed. In this study, *S. pneumoniae* was the most common etiology beyond the neonatal period and under 5 yr as well as in patients between 5 and 18 yr. PCV7 was introduced in 2003 in Korea. Because of insufficient vaccination coverage and slow implementation, decline in the number of cases of pneumococcal meningitis was not observed in this study. Further studies assessing the incidence of pneumococcal meningitis in post-vaccination period are needed.

N. meningitidis was the third common agent for last two decades in Korean children beyond the neonatal period, with relatively low incidence compared with the United States and European, African and Middle Eastern Asian countries (4, 12, 23-25, 28). The relative frequency of meningococcal meningitis has increased after the introduction of the Hib vaccine in the United States (21). Although meningococcus has contributed relatively less to bacterial meningitis in Korean children, watching changing incidence is important.

The mortality rate for bacterial meningitis in children reported in various countries ranged from 4% to 10% in more recent studies (4). Case-fatality rate in this study was greatest in pneumococcal meningitis similar to that shown in other studies (4, 21, 29). Death by *H. influenzae* meningitis was not found in our data. Reasons for this are that *H. influenzae* meningitis can be well recovered when early treatment, including the choice of adequate antibiotics, was started. Early use of dexamethasone can help to decrease inflammation of meninges and prevent fatal outcome. Transient and permanent complications were observed in 20% of patients in this report. This rate was comparable to other reports where 20-50% of survivors had serious and permanent sequelae such as epilepsy, mental retardation, deafness, learning impairment, sensory-motor deficit and cerebral palsy (29, 30).

Although our study demonstrated the trends and outcomes of bacterial meningitis in Korean children, some limitations of the study should be considered. This study included only the patients who were admitted to university hospitals and had lumbar punctures. And, antibiotic uses prior to hospitalizations could make it difficult to detect organisms by culture, especially before 2000 when antibiotics could be obtained without a doctor's prescription in Korea. These might result in underestimation of the number of bacterial meningitis cases. Another limitation is that we could not know the long-term sequelae of the patients because the final outcomes of the patients were determined at discharge or death.

In conclusion, in the last 10 yrs *S. agalactiae* and *E. coli* were the major etiologic agents of bacterial meningitis in neonates and infants below 3 months, and *S. pneumoniae*, *H. influenzae* and *N. meningitidis* in Korean children beyond 3 months. Establishment of a preventive strategy for *S. agalactiae* infection in neonates is required. The universal administration of Hib and pneumococcal conjugate vaccine should be adapted to the national immunization program. The nationwide epidemiologic surveillance should be continued to give invaluable information which will have a great influence in making important decisions on the national vaccination policy and to evaluate the efficacy of newly adapted vaccines.

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