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ORIGINAL ARTICLE

Evolving trends of neonatal and childhood bacterial meningitis in northern Taiwan

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Background: The epidemiology of bacterial meningitis varies in different areas, age groups, and times. To know the trend of neonatal and childhood bacterial meningitis in northern Taiwan, we performed this 29-year-long assessment.
Methods: Eligible patients were aged 18 years or younger, hospitalized in Mackay Memorial Hospital between 1984 and 2012, and proven by positive cerebrospinal fluid bacterial cultures. Analysis included the patient numbers and pathogens in different age groups, periods, complications, and outcomes.
Results: Males were predominant in all the age groups through the years. Almost half of the patients were in the neonatal period. Patient numbers went up in the early study period and declined after 1993—1997. Group B *Streptococcus* and *Escherichia coli* were the most common pathogens in neonates, whereas in childhood were *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib). Patient numbers of Group B *Streptococcus*, *S. pneumoniae*, and Hib meningitis declined in the late study period, but *E. coli* meningitis increased. The mortality rate decreased but sequela rate increased. Among the four most common pathogens, *S. pneumoniae* had the worst outcome and had highest mortality rate. All Hib meningitis patients survived, but their sequela rate was the highest.
Conclusion: This study provides an epidemiological data on trends of neonatal and childhood bacterial meningitis in northern Taiwan during the past 29 years, including male and neonatal

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predominance, decrease of total patient number in recent years, change of major pathogens, and declined mortality but raised morbidity.

Introduction

The main pathogens of bacterial meningitis are known to be different in different age groups, eras, and geographic areas. Group B *Streptococcus* (GBS), *Escherichia coli*, and *Listeria monocytogenes* are the most common causative organisms of neonatal bacterial meningitis in western countries,[1,2] but *L. monocytogenes* is hardly found in neonatal meningitis of Asian countries, including Taiwan.[3–6] *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae*, and *Neisseria meningitidis* are considered to be the three most common pathogens for childhood bacterial meningitis prior to introducing the specific vaccines. However, the incidence of Hib meningitis in Taiwan was found to be lower than that in western countries in 1992–1994.[7] Compared with some countries, meningococcal meningitis is infrequently reported in Taiwan. The annual incidence of meningococcal disease was below 0.001/100,000 population between 1980 and 1987 and increased only to 0.2 cases/100,000 population in 2001.[8] Vaccination frequently has great impact on specific infectious diseases. In France, the invasive Hib disease in children aged $<$ 5 years declined by 96% 15 years after the introduction of vaccination.[9] In Senegal, a near elimination of Hib meningitis burden was found after Hib conjugate vaccine was implemented into their routine infant immunization program.[10] Pneumococcal conjugate vaccine also has good results for decreasing disease burden.[11,12] There are some other factors that might influence the epidemiology of bacterial meningitis. Because epidemiology changes with time and place, knowing the local condition would be very important for clinicians. Herein, we review the data of proven bacterial meningitis in our pediatric patients during the past 29 years to reveal the trends of neonatal and childhood bacterial meningitis situations in our area.

Materials and methods

Patient selection

The patients in this study were selected from the administrative database of the Mackay Memorial Hospital, a medical center with around 200 pediatric beds in northern Taiwan. The bed number had only minor changes during the past three decades. This study was approved by the institutional review board of the hospital. The hospitalized patients aged 18 years or younger with a positive cerebrospinal fluid (CSF) bacterial culture results during the period from January 1984 to December 2012 were enrolled. Tuberculous meningitis was excluded. Patients diagnosed as having meningitis without bacteria isolated from the CSF were not included, even those who had elevated CSF cell counts, positive blood culture results, or clinical presentations of meningitis were excluded. The CSF cultures yielded normal skin flora (e.g., coagulase-negative staphylococci) considered to be contaminations were excluded unless CSF cell counts and clinical presentations fit the diagnosis of meningitis. Patients with evidence of congenital infections were also excluded.

Data collection

We searched the patients from both the diagnostic database and microbiological database to find eligible patients. The analyzed data included patients' age and sex, meningitis occurrence year, CSF pathogens, complications, and outcomes. If a patient had more than one spinal tap within an episode of meningitis, only the first CSF result was analyzed. If a patient had more than one episode of bacterial meningitis, i.e., recurrent meningitis, the findings were calculated separately in each episode.

Statistical analysis

According to their age, the patients were divided into four groups: $<$1 month; 1 month to $<$1 year, 1–6 years, and 7–18 years. We further divided the 29 years into 6 periods, from 1984 to 1987, then every 5 years in each period. The outcomes of the patients were classified into death, having sequelae, recovery, and loss of follow-up. Sequelae were defined as having consequent physical or psychological morbidities lasting for $>$6 months after the meningitis episode. Recovery was defined as survival without sequelae.

We compared the patient numbers in different age groups and periods, pathogens in different age groups and periods, complications and outcomes in different age groups, periods, and pathogens. The lost follow-up patients were excluded from comparison of mortality rates. The sequela rates and recovery rates were calculated only in survivors.

Significant differences among different year periods, age groups, and pathogens were determined by χ^2 or Fisher exact test for comparison. Trends of patient numbers, pathogens, and outcomes during the study period were tested. All reported $p < 0.05$ were considered statistically significant. Statistical analyses were performed using SPSS version 20.0 software (SPSS, Inc., Chicago, IL, USA).

Results

Characteristics of patients

A total of 323 episodes of proven pediatric bacterial meningitis were enrolled during the 29-year period. The male to

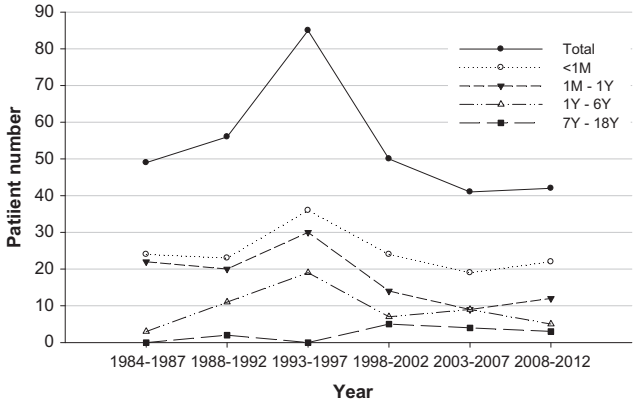

Figure 1. Patient numbers in different year periods of 323 cases of pediatric bacterial meningitis.

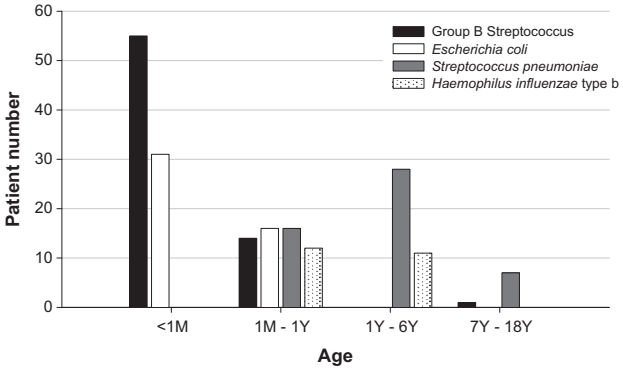

Figure 2. Patient numbers of the four most common pathogens of pediatric bacterial meningitis in different age groups.

female ratio was 1.69. The male predominant trend was found in all different age groups. Near half of the patients were aged <1 month (148 patients, 45.8%); 107 patients (33.1%) were aged 1 month to <1 year; 54 patients (16.7%) were aged 1—6 years; and 14 patients (4.3%) were aged 7—18 years.

The patient numbers in different age groups during the study period are shown in Fig. 1. The total patient numbers had a mild decreasing trend in the past 10 years; i.e., >50 episodes occurred in each 4—5-year period prior to 2003 and dropped to near 40 episodes in the past two 5-year periods. There was a significant decreased trend ($p = 0.025$) in patients aged <1 year, and an increased trend ($p = 0.004$) in patients >7 years. There was a surge of patient number in 1995. Among the 28 episodes of that year, 16 occurred in neonates and 10 were GBS meningitis but not from an outbreak.

Trends of pathogen change

GBS was the most common pathogen (70 episodes, 21.7%), followed by *S. pneumoniae* (51 episodes, 15.8%), *E. coli* (47 episodes, 14.6%), Hib (23 episodes, 7.1%), group A streptococci (15 episodes, 4.6%), *Enterobacter cloacae* (13 episodes, 4.0%), *Klebsiella pneumoniae* (12 episodes, 3.7%), *Elizabethkingia meningosepticum* (12 episodes, 3.7%), enterococci (10 episodes, 3.1%), and *N. meningitidis* (9 episodes, 2.8%). The common pathogens of different age groups are shown in Table 1 and the four most common pathogens in Fig. 2. GBS and *E. coli* were the most common

Table 1 Pathogens of 323 cases of pediatric bacterial meningitis in different age groups

Pathogen	<1 mo	1 mo—<1 y	1—6 y	7—18 y	Total
Gram-positive bacteria	**78**	**46**	**35**	**9**	**168**
Group B streptococcus	55	14	0	1	70
Streptococcus pneumoniae	0	16	28	7	51
Group A streptococci	6	6	3	0	15
Enterococcus spp.	6	3	1	0	10
Streptococcus bovis	4	1	1	0	6
Other Gram-positive organisms[a]	7	6	2	1	16
Gram-negative bacteria	**70**	**61**	**19**	**5**	**155**
Escherichia coli	31	16	0	0	47
Haemophilus influenzae type b	0	12	11	0	23
Enterobacter cloacae	6	4	2	1	13
Klebsiella pneumoniae	6	1	4	1	12
Elizabethkingia meningosepticum	10	1	1	0	12
Neisseria meningitidis	1	6	0	2	9
Proteus mirabilis	6	1	0	0	7
Pseudomonas aeruginosa	2	4	0	0	6
Haemophilus parainfluenzae	2	2	0	1	5
Salmonella spp.	0	4	0	0	4
Alcaligenes spp.	0	4	0	0	4
Plesiomonas spp.	0	3	1	0	4
Other Gram-negative organisms[b]	6	3	0	0	9

[a] Other Gram-positive organisms included *Listeria monocytogenes*, other *Streptococcus* spp. and *Staphylococcus* spp.
[b] Other Gram-negative organisms included *Acinetobacter* spp., *Enterobacter aerogenes*, *Sternotrophomonas maltophilis*, *Klebsiella oxytoca*, and *Moraxella* spp.

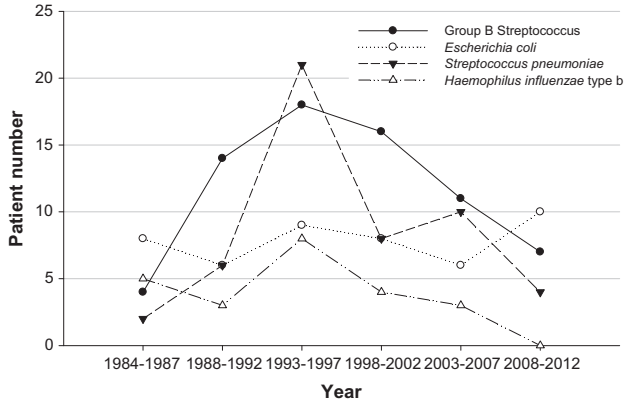

Figure 3. Year distribution of the four most common pathogens of pediatric bacterial meningitis.

two pathogens of neonatal meningitis (37.2% and 20.9%); they were also common pathogens up to age 1 year and accounted for 27.1% and 18.4% in the patients of that age, respectively. There was no *S. pneumoniae* or Hib meningitis found below the age of 1 month, but they increased afterward. After age 1 year, *S. pneumoniae* and Hib became the dominant pathogens (*S. pneumonia*, 35 episodes, 51.5%; Hib, 11 episodes, 16.2%), but no Hib meningitis patients aged $>$ 6 years were found. There were nine patients (2.8%), distributed in different age groups, got *N. meningitidis* infection.

The year distribution of four predominant pathogens was shown in Fig. 3. The patient number of GBS in 1995 was extraordinarily high, but no significant change otherwise. The number of *E. coli* patients remained stable during the 29 years and became larger than that of GBS in the past 5-year period. The number of *S. pneumoniae* patients peaked in 1994—1997 then decreased, and no patient was found in 2011 or 2012. Apart from a surge in 1995 (5 patients), Hib meningitis occurred evenly, but there were no further patients after 2004. Although changes were noted within the study period, no statistically significance was found.

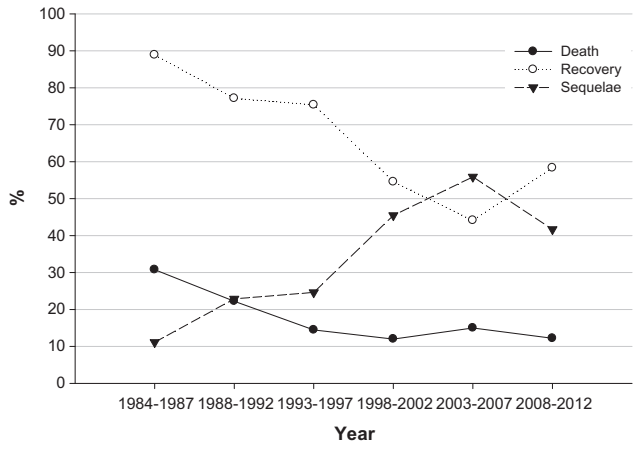

Figure 4. Mortality rates of total followed-up pediatric bacterial meningitis patients, and recovery and sequela rates of survivors in different year periods.

Complications and outcomes

Fewer than half of the patients (147 patients, 45.5%) had no complications. The common complications included seizure (61 patients, 18.9%), hydrocephalus (45 patients, 13.9%), subdural empyema (40 patients, 12.4%), and hearing impairment (38 patients, 11.8%). The complication rates in different age groups and year periods had no significant fluctuation.

Excluding the 32 patients who were lost to follow-up (9.9%), 50 patients (17.2% of 291 patients) died. Among the 241 survivors, 160 (66.4%) recovered completely, and 81 (33.6%) had sequelae. There was no significant difference of the outcome ratio in different age groups. The mortality rate decreased through the years from 30.8% in 1984—1987 to 12.2% in 2008—2012 ($p = 0.023$). Nonetheless, the sequela rate in survivors increased from 11.1% in 1984—1987 to 41.7% in 2008—2012 ($p < 0.001$), and the recovery rate decreased ($p = 0.028$; Fig. 4).

Among the four most common pathogens, *S. pneumoniae* had the worst outcome ($p = 0.016$) and had the highest mortality rate (26.7%). The other mortality rates were *E. coli* (19.0%), and GBS (8.7%). All Hib meningitis patients survived, but their sequela rate was the highest (41.2%). The lowest completely recovery rate in survivors (48.5%) was found in *S. pneumonia* meningitis patients. Besides the four most common pathogens, we also compared the outcomes of other Gram-positive and Gram-negative organisms as shown in Fig. 5. The outcome in other Gram-positive organisms was good ($p = 0.046$), the overall mortality rate was 9.5%. Other Gram-negative organisms had a relatively bad outcome ($p = 0.032$); the mortality rate was 27.3%.

Discussion

In this 29-year-long survey we found several stable conditions and several changing trends of neonatal and childhood meningitis in our hospital. Numerous factors may contribute to the changes of the epidemiology, including birth rates, vaccination administration, prenatal maternal vaginal bacterial screening, national health insurance, new antibiotic agents, and novel patient management.

The male-to-female ratio in our patients is higher than that of the general population. This indicates that males are prone to have bacterial meningitis. Similar sex discrepancy in meningitis is found in other countries.[13,14] Sex-related differences in reported morbidity for bacterial infections were documented among different age groups. The reasons may be related to underlying development processes, including those affecting the immune, endocrine, and reproductive systems, or differences in reporting rates.[15]

Our hospital has a neonatal intensive care unit caring for neonates not only born in our hospital but also referred from other hospitals. The high proportion of neonates in our study may be partly related to that. A significant trend of decrement of patient number with increasing age is noted. In the Japanese nationwide survey, children younger than 1 year accounted for the majority of cases (51.2%), and the same trend of age relationship was reported.[13]

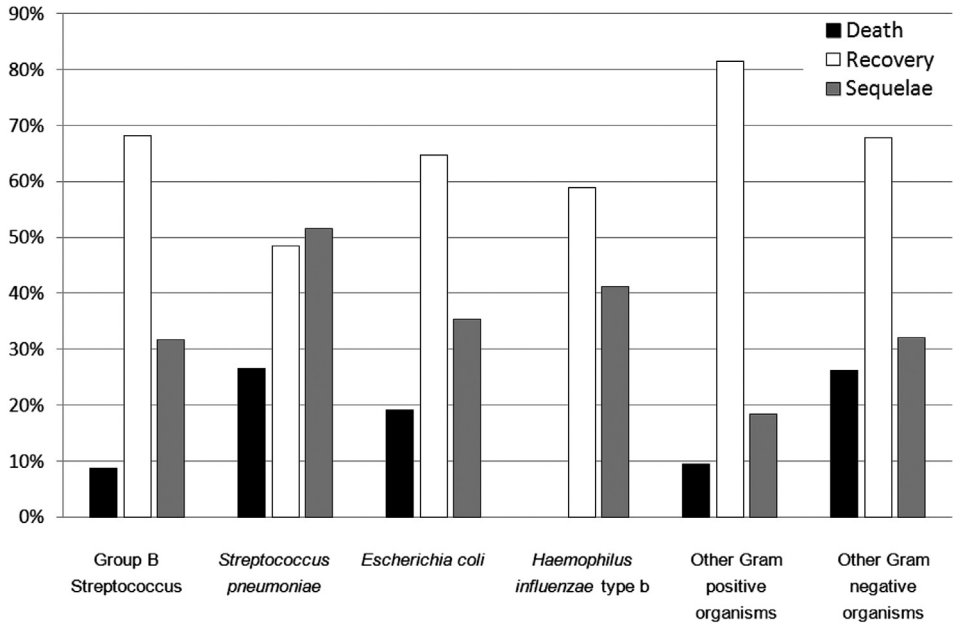

Figure 5. Outcomes of pediatric bacterial meningitis of different pathogens.

Unlike in the USA, where the rate of bacterial meningitis declined by 55% in the early 1990s,[16] our patient number does not have a such significant decline. The annual newborn numbers in Taiwan has dropped dramatically in recent years. The crude birth rate was 19.6/1000 in 1984 and became 8.48/1000 in 2011.[17] Taiwan's national health insurance started in 1995; before then, some neonates and children with poor prognosis might be given up due to the heavy unaffordable medical expense for young parents. We observed a surge in patient number in that year and a decreasing slope thereafter. Birth rate and economic supporting system may have great influence for the change of patient number.

Vaccines are available for some major meningitis pathogens, such as Hib, *S. pneumoniae*, and *N. meningitidis*. Single Hib vaccine was introduced to Taiwan prior to 2000 at the parents' own expense. As a component of self-paid DTaP-Hib-IPV five-in-one mixed vaccine, Hib vaccine was remarketed in 2002 and became a government-paid vaccine in 2010. Hib meningitis was not common prior to vaccination and disappeared after 2004 in our study. The cost-effectiveness of Hib vaccine in Taiwan may be not as good as in some other countries,[18,19] but its intangible benefits could put it into the universal vaccination schedule as some low-incidence countries.[20]

In Taiwan, the pneumococcal conjugate vaccine has been available as a self-paid vaccine since late 2005. High-risk pneumococcal children were provided with the vaccine at government expense from July 2009. This vaccine is expensive and self-payment has been accepted by parents gradually only in recent years. We did not have pneumococcal meningitis patients in the past 2 years. The cost-effectiveness of the vaccine has been analyzed and universal vaccination has been scheduled in Taiwan.[21]

GBS and *E. coli* remained the two most common pathogens of neonatal meningitis through the study period, but *E. coli* overcame GBS and became the most common pathogen of neonatal meningitis in the past 5-year period. Maternal GBS screening and *intra partum* antibiotic prophylaxis were implemented in our hospital in 2004 and became government-paid in 2012. Like early-onset neonatal sepsis,[22] this strategy is effective in decreasing the incidence of GBS meningitis, but an increase of *E. coli* infection is noted.

The burden of meningococcal meningitis is not heavy in Taiwan: $<3\%$ of our patients were infected by meningococcus. The meningococcal vaccine, although its usefulness has been proven in many countries,[23] is not the priority vaccine for the government budget in Taiwan at present. Only four *Salmonella* meningitis patients were recorded in our patients. Environmental hygiene and public health improvement may be important factors.[24] *L. monocytogenes* is an important pathogen for neonatal meningitis in many areas,[1,16,25] but not in Asian and some developing countries.[3,4,26] Only two neonates in our study got *L. monocytogenes*, presumably related to low availability of the usual contaminated dietary sources.[26]

The incidences of complications and prognosis depend on the era and the duration of follow-up.[27] Our complication incidence was high.[27,28] The mortality rate of our patients was also high,[13,28] but improved from almost one-third in the early period to one-eighth at the end of the study. However, the sequela rate increased from near one-tenth to two-fifths. Similar to other reports,[27] *S. pneumoniae* meningitis has high mortality and morbidity in this study. Although no Hib meningitis patients died, two-fifths of them had sequelae. Neonates with GBS meningitis had a better outcome than those with *E. coli* meningitis. Excluding the four common pathogens, meningitis caused by other Gram-negative bacteria had a worse outcome than other Gram-positive organisms. Among the other Gram-negative group, meningitis caused by *Pseudomonas aeruginosa, Proteus mirabilis, E. cloacae, K. pneumoniae,* and *Salmonella* had an especially high mortality rates (all above 25%).

Due to the diversity and complexity of antibiotic prescription, we could not analyze the impact of new

antibiotic agents. We also could not evaluate other novel management for meningitis. Because these data are from a single hospital, they are unlikely to represent the exact epidemiology of the whole area. As there is still no national pediatric bacterial meningitis surveillance in Taiwan, our results could reveal the tendency to some extent and offer information for managing this severe infectious disease.

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