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Characteristics of neonatal bacterial meningitis in a teaching hospital in Taiwan from 1984-1997

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During the period from 1984 to 1997, 85 bacterial meningitis neonates with positive cerebrospinal fluid cultures were treated. The ages of these patients ranged from 1 to 28 days. The male to female ratio was 1.7 to 1. The most common causative agent was group B ß-hemolytic streptococci (GBS, 31.8%), followed by *Escherichia coli* (20%), *Proteus mirabilis* (7.1%), *Enterobacter cloacae* (5.9%), other *streptococci* excluding *Streptococcus pneumoniae* (5.9%), *Chryseobacterium meningosepticum* (5.9%), enterococci (4.7%), and *Klebsiella pneumoniae* (3.5%). Among the 85 patients treated, 51 (60%) were younger than 7 days old. Among them, dyspnea was the most common clinical manifestation. In contrast, fever and diarrhea were seen more frequently in neonates with late onset of disease (after seven days of age). Ampicillin and cefotaxime were the most commonly used antibiotics. The most frequently encountered complications were hydrocephalus and seizures. Since 1991, GBS has overtaken *E. coli* as the leading cause of neonatal bacterial meningitis. This was accompanied by a fall in the mortality rate, but a sustained high incidence of complications and sequelae. The results of this study highlight the importance of developing strategies to prevent group B streptococcal infection.

Key words: Group B streptococci, neonatal bacterial meningitis, prevention

Bacterial meningitis is an important cause of illness and death in infancy. It is more common in the neonatal period than at any other time of life. Although the importance of establishing countermeasures against this infectious disease in neonates is widely accepted, there have been few epidemiologic studies in Taiwan. Changes in the spectrum of organisms causing neonatal meningitis during the last two decades have been reported in the US and Australia, with group B streptococci (GBS) displacing *Escherichia coli* as the leading cause [1]. In Taiwan, several studies have shown that gram-negative enteric bacilli were the most common pathogens of neonatal meningitis in the 1960s and 1970s. However, the organism most frequently responsible has changed from *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* to *E. coli* [2-5]. Since the early 1980s, GBS has been the most common pathogen of bacterial meningitis in newborns and in early infancy [4,6,7]. The present study sought to describe trends in neonatal bacterial meningitis over a 14-year period in a teaching hospital in Taiwan.

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Materials and Methods

We reviewed the medical records and analyzed the data of all infants with a diagnosis of bacterial meningitis aged from 1 to 28 days of age, who were admitted to the pediatric ward of Mackay Memorial Hospital during the 14-year period from January 1984 to December 1997.

A diagnosis of bacterial meningitis was based on a positive cerebrospinal fluid culture. Septicemia was diagnosed by positive blood culture. Because all patients had an onset of symptoms within 72 h of admission, nosocomial infections were ruled out. Information on age, sex, onset of symptoms, predisposing factors, clinical manifestations, and outcome were analyzed. According to the time of onset of symptoms, the patients were divided into early onset disease (EOD) and late onset disease (LOD) categories. EOD was defined as the onset of symptoms/signs in an infant younger than 7 days of age. LOD was defined as the onset of symptoms/signs in an infant equal to or older than 7 days of age. To identify trends in neonatal meningitis, cases were analyzed on the basis of two periods of time: 1980s (1984-90) and 1990s (1991-97).

The statistical analyses were performed with Fisher's exact test or chi square test as appropriate. A value of p less than 0.05 was considered statistically significant.

Results

A total of 85 cases of neonatal bacterial meningitis were diagnosed and treated during the 14-year study period. Among them, 53 (62.4%) were male and 32 (37.6%) were female, with a male to female ratio of 1.7 to 1. Forty-one cases (60%) were younger than 7 days of age (EOD group) and 34 (40%) were equal to or older than 7 days of age (LOD group); 42 (49.4%) cases occurred in the 1980s and 43 (50.6%) in the 1990s. The most common predisposing factor was prematurity, followed by cesarean section. Prematurity occurred more frequently in EOD than that in LOD (33.3% vs. 11.8%; $p = 0.023$). Fever, poor appetite, dyspnea, cyanosis, jaundice, and convulsion were the most frequently encountered symptoms at initial examination. Dyspnea was seen more frequently in EOD than that in LOD (31.4% vs. 8.8%; $p = 0.017$). However, fever and diarrhea were more common initial symptoms in LOD than that in EOD, with a p value of 0.02 and 0.026, respectively (Table 1). The causative microorganisms were listed in table 2.

During the early period (1984-90), the most frequently reported isolate was *E. coli*, followed by GBS. In the late period (1991-97), GBS displaced *E. coli* as the leading cause of neonatal bacterial meningitis. The increase in the case numbers of GBS was statistically significant between the early and late periods (19.1% vs. 44.2%; $p = 0.019$). The case numbers of both EOD and LOD caused by GBS increased in the late period compared to the early period (from four cases to eight cases with EOD and four cases to 11 cases with LOD). There was a decrease in the number of cases of gram-negative rods in the 1990s compared to that of the 1980s (64.3% vs. 35.3%). Blood cultures were positive in 74.1% of the 85 patients; GBS in 88.9%, *E. coli* in 58.8%, and *P. mirabilis* in 100%.

Ampicillin and cefotaxime were the most frequently used antibiotics, with usage rates of 76.5% and 52.9%

Table 1. Clinical manifestations of early and late onset neonatal bacterial meningitis

Symptom/sign	EOD (n = 51) [a] No. of cases (%)	LOD (n = 34) [b] No. of cases (%)	*p*
Fever	27 (52.9)	29 (85.3)	0.002[c]
Poor appetite	13 (25.5)	12 (35.3)	0.344
Dyspnea	16 (31.4)	3 (8.8)	0.017[c]
Cyanosis	14 (27.5)	4 (11.8)	0.107
Jaundice	11 (21.6)	4 (11.8)	0.384
Convulsion	7 (13.7)	5 (14.7)	1.000
Vomiting	5 (9.8)	6 (17.6)	0.335
Irritability	3 (5.9)	7 (20.6)	0.081
Diarrhea	2 (3.9)	7 (20.6)	0.026[c]

[a]The onset of symptoms/signs in an infant younger than 7 days of age
[b]The onset of symptoms/signs in an infant equal to or older than 7 days of age
[c]Fisher's exact test, $p < 0.05$

Table 2. Microorganisms causing bacterial meningitis in neonates

Microorganism	1984-1990 (n = 42) No. of cases (%)	1991-1997 (n = 43) No. of cases (%)	*p*
Group B streptococci	8 (19.1)	19 (44.2)	0.019[a]
Escherichia coli	10 (23.8)	7 (16.3)	0.427
Proteus mirabilis	4 (9.5)	2 (4.7)	0.433
Chryseobacterium meningosepticum	2 (4.8)	3 (7.0)	1.000
Enterobacter cloacae	3 (7.0)	2 (4.7)	0.676
Other streptococci	3 (7.0)	2 (4.7)	0.676
Enterococci	3 (7.0)	1 (2.3)	0.360
Klebsiella pneumoniae	3 (7.0)	0 (0.0)	ND[b]
Others[c]	6 (14.3)	7 (16.3)	ND[b]

[a]Fisher's exact test, $p < 0.05$
[b]Not done
[c]Includes MRSA (2), *Streptococcus bovis* (2), *Gemella morbillorum* (2), *Haemophilus influenzae* (1), *Pseudomonas aeruginosa* (1), *Acinetobacter* species (1), *Burkholderia cepacia* (1), *Plesiomonas shigelloides* (1), *Staphylococcus epidermidis* (1), *Bacteroides fragilis* (1)

Table 3. Outcome of neonatal bacterial meningitis

	1984-1990 (n = 42) No. of cases (%)	1991-1997 (n = 43) No. of cases (%)	Total (n =85) No. of cases (%)
Died	18 (42.9)	7 (16.3)	25 (29.4)
Complete recovery	21 (50.0)	30 (69.8)	51 (60.0)
Sequelae	3 (7.1)	6 (14.0)	9 (10.6)

of cases, respectively. Gentamicin and penicillin were the third and fourth most commonly used antibiotics, with rates of 37.6% and 28.2%, respectively. All strains of GBS were susceptible to penicillin on disk diffusion testing throughout the 14-year study period. Comparison of the choice of antibiotics used in the 1980s and 1990s showed that the frequency of using cefotaxime increased in the 1990s. In fact, cefotaxime was the most commonly chosen antibiotic during the 1990s.

Complications included hydrocephalus in nine patients, seizures in six, hearing impairment in two, subependymal cyst in two, subdural empyema in one, brain abscess in one, cystic periventricular leukomalacia in one, and neurogenic bladder in one. The number of complications in the 1990s was 3.6 times higher than that in the 1980s (18/5). GBS accounted for 47.8% of the causative organisms in patients with complications, with seizure being the most common GBS-related complication (5/11). *C. meningosepticum* accounted for 17.4% of complications, all of which involved hydrocephalus (3/3). Table 3 shows the outcome of neonatal bacterial meningitis. The number of cases involving mortality and sequelae differed significantly between the early (1984-90) and late (1991-97) periods (Chi square, $p = 0.025$). The mortality rate decreased significantly (odds ratio = 3.67, early period *vs.* late period), and the number of sequelae increased significantly in the late period (odds ratio = 0.71, early period vs. late period). There was a striking male preponderance in fatal cases (83.3% male, 16.7% female). The mortality rate in neonates with gram-negative meningitis was 2.6 times higher than that in neonates with gram-positive meningitis (18/7). Cases with EOD accounted for 88% (22/25) of fatalities .

Discussion

In the mid 1970s, hospital-based surveys suggested that GBS had replaced *E. coli* as the leading cause of neonatal sepsis and meningitis, and had also become a major cause of maternal peripartum infections, such as chorioamnionitis, postpartum endometritis, urinary tract infections, and peripartum bacteremia [8-11]. Several studies in Taiwan showed that gram-negative enteric bacilli were the most common pathogens of neonatal meningitis in the 1960s and 1970s. The leading causative organisms changed from *P. aeruginosa* and *K. pneumoniae* to *E. coli* during this period [2-5]. During the early period of our study (1984-1990), the frequency of meningitis due to *E. coli* exceeded that of GBS. However, the number of cases of GBS meningitis increased significantly in the late study period (1991-1997), with GBS overtaking *E. coli* as the leading cause of neonatal meningitis in our hospital. The reason for this change is not known.

Bacterial meningitis carries a high rate of morbidity in the neonatal period. Reported case fatality rates have ranged from 66% in the beginning of the antibiotic era to 20% to 50% in more recent studies in developed countries [1]. In the present study, the mortality rate was 42.9% in the early period (1984-1990) and fell to 16.3% in the late period (1991-1997). Franco *et al* described that the mortality rate in neonates with gram-negative meningitis was almost three times higher than that of neonates with gram-positive meningitis [12], and the results of the present study support these findings. While improvements in early detection and antibiotic treatment have reduced the mortality rates of neonatal meningitis, there has been little resulting impact on acute care costs and long-term morbidity. In addition, the frequency of complications and sequelae have increased since 1991, which may be a result of the improved survival rates. These findings should serve as a reminder of the importance of prevention of neonatal meningitis.

GBS disease is potentially preventable with antibiotic prophylaxis or immunization in women of childbearing age. In 1996, the Centers for Disease Control and Prevention (CDC) [13], the American College of Obstetrics and Gynecology (ACOG) [14], and the American Academy of Pediatrics (AAP) [15] issued consensus guidelines on the prevention of perinatal GBS disease. The common denominator among these guidelines is the early identification of GBS bacterial infection in pregnant women. The procedure for isolation of GBS from prenatal specimens using a culture of selective broth media has well been described [16]. The use of selective broth media is

critical to the effectiveness of the prenatal screening process, as it increases the detection rate by 50% [17]. A substantial reduction in the incidence of early onset GBS infection is likely to occur if intrapartum antimicrobial prophylaxis is instituted. However, neonatal meningitis caused by GBS occurs more commonly in late onset than that in EOD. Prevention of late onset neonatal GBS meningitis depends upon the development and use of effective, multivalent GBS vaccines. At present, the following serotypes of GBS are recognized: Ia, Ib, Ia/c, II, III, IV, V, and VI. Contemporary surveys have demonstrated some shift in the distribution of serotypes in the past decade, with serotypes Ia and III remaining predominant in the isolates of infants, while the frequency of type II infection has diminished and type V has emerged [18].

Presumptive antimicrobial therapy of neonatal bacterial meningitis should include ampicillin and cefotaxime unless staphylococci are more likely to be the responsible pathogen, which would be an indication for the use of vancomycin. If GBS is isolated, penicillin G is usually the first choice. In the present study, all strains of GBS were susceptible to penicillin. Liu *et al* suggested the use of a higher dosage of penicillin based on the results in a previous series in Taiwan because of the finding of higher minimal inhibitory concentrations in clinical isolates [19]. *C. meningosepticum* is almost uniformly resistant to empiric antibiotics. Drugs that have been used alone or in combination with some success in the treatment of neonatal bacterial meningitis include erythromycin, vancomycin, trimethoprim-sulfamethoxazole, and rifampin. Piperacillin was also suggested to be effective by Lin *et al* [20]. The duration of antibiotic therapy for GBS is 14 to 21 days. Treatment of gram-negative meningitis should be continued for 21 days or for at least 14 days after sterilization of the CSF.

In Taiwan, a decreased incidence of early onset GBS disease was noted by Yang *et al* [21]. In the present study, the number of cases of both early onset and late onset GBS meningitis increased in the 1990s compared to that in the 1980s. Whether the intrapartum chemoprophylaxis is a widely adopted procedure is doubtful. In addition, it may be inadequately or inappropriately administered (e.g. by oral antibiotics). Further study is needed to determine the population-based rates of GBS disease and the cost-effectiveness of GBS prevention strategies. Clinicians should be aware that infections due to penicillin-tolerant organisms have been reported [22,23]. Other efforts should be focused on increasing awareness of GBS disease as a preventable disease, increasing the use of selective broth media for culture, and detecting the serotypes of GBS to improve vaccine formulations.

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