CLINICAL PROFILE OF MENINGITIS AMONG FILIPINO NEONATES: A TWELVE-YEAR COLLABORATIVE REVIEW

ANA MARIE R. MORELOS, M.D. AND SALVACION R. GATCHALIAN, M.D.

U.P.-Philippine General Hospital, Taft Ave., Manila and Research Institute for Tropical Medicine, Department of Health, Alabang, Muntinlupa, Metro Manila

ABSTRACT

Bacterial meningitis is a common cause of morbidity and mortality among infants in developing countries. Because of the limited data on Filipino neonates, this retrospective study was undertaken to identify the etiologic agents and to describe the clinical presentation of neonatal meningitis. Of the 290 charts of patients admitted from July 1982 to December 1994 with the diagnosis of sepsis and meningitis that were reviewed, 32 met the inclusion criteria for purulent meningitis. The most frequent etiologic agents were Group B streptococci and gram negative enteric bacilli: E. coli, Klebsiella, non-typhoidal Salmonella, Enterobacter, Acinetobacter and Pseudomonas. Poor suck, seizures and fever were the most prominent signs and symptoms. More than half of patients presented with peripheral leucocytosis. About 70% had a favorable outcome after 10-21 days of antibiotic therapy consisting of Ampicillin or Penicillin plus and aminoglycoside. The rest (30%) were mortalities, half of which were attributed to gram negative bacillary meningitis. Considering the etiologies and outcomes of this series, a combination of Penicillin and an aminoglycoside (with Penicillin and a broad spectrum 3rd generation cephalosporin as an alternative) is still the most effective empiric regimen for most cases of neonatal meningitis in the Philippines.

INTRODUCTION

Bacterial meningitis, specially when it afflicts the neonate is potentially fatal. Its presentation is quite subtle but its consequences are devastating if misdiagnosed. Though long recognized since the time of Hippocrates and its cause known since the latter quarter of the 19th century, bacterial meningitis among neonates was invariably fatal prior to the advent of antimicrobial agents. With the introduction of sulfonamides in the 1930's, mortality significantly dropped and for a time, after chloramphenicol was introduced, it was thought that the problem of neonatal meningitis would be solved completely. However, it has now been evident that despite advances in antibiotics and intensive care management, case fatality rates and long term morbidity remain unacceptably high.

All over the world, bacterial meningitis occurs at a frequency of between 20-100 per 100,000 live births in the newborn period.[1] In developed countries, mortality is as high as 20-40% with long-term neurologic damage in 30-50%.[2,3,4] In developing countries such as Thailand and the African nations, bacterial meningitis in neonates is associated with a 41-49% mortality rate and the incidence of neurologic sequelae among survivors is 38%.[5] In the Philippines, bacterial meningitis is the 10th leading cause of mortality in Filipino infants and remains a common cause of morbidity in all age groups.[6] In both developed and developing countries, there is limited information on the epidemiology of neonatal meningitis due to difficulties in establishing comprehensive systems of notification and due to widespread underreporting. Likewise, in a country such as the Philippines where resources are limited and where laboratory tests for qualitative, quantitative and microbiologic examinations of the cerebrospinal fluid (CSF) are inaccessible to physicians, the approach to decreasing morbidity and mortality relies heavily upon inaccessible to physicians, the approach to decreasing morbidity and mortality relies heavily upon comprehensive and reliable local data on the clinical profile and epidemiology of neonatal meningitis. Consequently, with data made available, recommendations for rational and effective empiric antimicrobial treatment can be established. This twelve-year retrospective study was thus undertaken to identify the etiologic agents and to describe the clinical presentation of bacterial meningitis among Filipino neonates.

SUBJECTS, DEFINITIONS AND METHODS

The records of 290 neonates admitted to the Research Institute for Tropical Medicine (RITM) with the clinical diagnosis of neonatal sepsis and/or neonatal meningitis during the 12-year period from July, 1982 through December, 1994 were reviewed. The RITM is a 45-bed hospital in Metro Manila for infectious disease cases. About 80-90% of its admissions are walk-in pediatric patients or referrals from other tertiary care facilities all over the country.

The inclusion criteria for definite meningitis and probable meningitis are listed in Tables 1 and 2. Definite bacterial meningitis was defined as 1) positive bacterial culture from the cerebrospinal fluid (CSF) or positive gram stain of the CSF or positive counter

immunoelectrophoresis or latex agglutination test and 2) CSF pleocytosis of greater than 32 white blood cells with CSF protein levels greater than 45 g/dl and CSF sugar less than 2.2 mmol/l or less than 30% of the random blood sugar level.

Table 1. Inclusion Criteria for Definite Meningitis

1)	positive in 1 or more:	
	CSF culture	
	CSF Gram stain	
	CSF CIE or latex agglutination	
	and	
2)	abnormal CSF Q/Q findings:	
	pleocytosis > 32 wbc	
	increased Protein	> 45 mg/dl
	decreased Sugar	< 2.2 mmol/l
		or
		< 30% of RBS

Table 2. Inclusion Criteria for Probable Meningitis

1)	Autopsy findings of suppurative meningitis	
	or	
2)	at least 2 clinical and 3 laboratory parameters	
	Clinical:	
	a. meningeal signs and symptoms	
	b. extra-CNS focus of infection	
	c. neurologic abnormalities aside from a.	
	d. apparent response to treatment clinical/laboratory improvement attributed to antibiotic therapy	
	Laboratory:	
	a. peripheral leucocytosis or neutrophilia	
	b. CSF pleocytosis > 32 wbc	
	c. increased CSF protein	> 45 mg/dl
	d. decreased CSF sugar	< 2.2 mmol/l
	or	< 30% of RBS

On the other hand, probable bacterial meningitis was defined as 1) autopsy findings of suppurative meningitis or 2) at lease 2 clinical and 3 laboratory parameters. The clinical parameters included meningeal signs and symptoms, extra-CNS focus of infection or other neurological abnormalities and apparent response to treatment. The laboratory parameters were peripheral leucocytosis or neutrophilia, CSF pleocytosis, increased CSF protein and depressed CSF sugar levels.

The 32 neonates that met the inclusion criteria were analyzed for sex, laboratory studies, bacterial etiology, presenting features and outcome.

RESULTS

During the 12-year period encompassed by this study, there were 32 cases (11%) of neonatal meningitis identified among 290 diagnosed cases of neonatal sepsis with a male to female ratio of 3:1 (Table 3). Before the seventh day of life, 17 (53.1%) presented with early-onset bacterial meningitis (Table 4). Seven (41.2%) of the cases of early-onset meningitis had identifiable etiologic agents: E. coli (2), Group B Streptococcus (GBS) (1), P. aeruginosa (1), Salmonella E (1), A. anitratum (1), E. cloacae (1). Among the late-onset meningitis cases, 48% were attributed to GBS (2), Klebsiella (2), Salmonella B (1), and S. albus (1). The predisposing factors and associated conditions that might have led to neonatal meningitis were identified in 9 (28%) cases: chorioamnionitis and other maternal infections (3), PROM (2), myelo-meningocoel (2) and omphalitis (2).

Table 3. No. of Cases of Neonatal Meningitis by Sex

	Definite Meningitis	Probable Meningitis	Total
male	9 (28.1%)	15 (46.9%)	24 (75.0%)
female	4 (12.5%)	4 (12.5%)	8 (25.0%)
total	13 (40.6%)	19 (59.4%)	32 (100%)

Table 4. Age of Onset of Meningitis

	Definite Meningitis n = 13 (%)	Probable Meningitis n = 19 (%)	Total n = 32 (%)
0-7 days	8 (25.0%)	9 (28.1%)	17 (53.1%)
> 7 days	5 (15.6%)	10 (31.3%)	15 (46.9%)

In most cases of neonatal meningitis, the signs and symptoms are non-specific and in this series, the most common physical findings in decreasing frequency were poor feeding followed by seizures, fever and poor activity. Other less common findings were jaundice, respiratory distress, bulging fontanel, cyanosis and diarrhea (Table 5).

Table 5. Clinical Picture of Neonates with Bacterial Meningitis

	Definite Meningitis n = 13 (%)	Probable Meningitis n = 19 (%)	Total n = 32 (%)
Poor feeding	7 (21.8%)	18 (56.3%)	25 (78.1%)
Seizure	7 (21.8%)	13 (40.6%)	20 (62.4%)
Fever	7 (21.8%)	10 (31.3%)	17 (53.1%)
Poor Activity	5 (15.6%)	9 (28.1%)	14 (48.7%)
Jaundice	8 (25.0%)	5 (15.6%)	13 (40.6%)
Respiratory Distress	5 (15.6%)	6 (18.8%)	11 (34.4%)
Bulging/Tense Fontanel	4 (12.5%)	7 (21.9%)	11 (34.4%)
Cyanosis	4 (12.5%)	4 (21.9%)	8 (25.0%)
Diarrhea	2 (6.2%)	6 (18.8%)	8 (25.0%)

Initial laboratory examination of the 32 cases upon admission revealed that 18.7% had anemia of less than 10 gm/dl hemoglobin levels. Leucopenia of less than 5,000 peripheral leucocyte count was seen in 6.3% while leucocytosis of more than 12,000 peripheral leucocyte count was seen in 25%.

CSF cultures were positive in 13(40%) of all cases and 8(61%) of these patients had concomittant bacteremia. In all cases, the blood isolates were the same as the CSF isolates (Table 6). Of the 13 cases with positive CSF cultures, only 5 yielded positive gram stains. The most common causative agents are similar to those reported by other workers in 3rd world countries.[5, 6] Gram-negative enteric bacilli accounted for 70% of isolates while the rest (30%) were gram-positive cocci. Listeria monocytogenes as a causative agent was not seen in this series. Only 6(18.8%) patients manifested acute complications: Hydrocephalus(3), sudural empyema(1), ventriculitis(1) and intraventricular hemorrhage(1).

Table 6. Microbiology and Outcome of Definite Bacterial Meningitis

Etiologic agents	(+) CSF culture n = 13	(+) Blood culture n = 8	Outcome died n = 6	Outcome improved n = 7
Group B Streptococci	3	2	0	3
E. coli	2	1	1	1
Klebsiella pneumoniae	2	1	2	0
Salmonella B	1	1	1	0
Salmonella E	1	1	0	1
Pseudomonas aeruginosa	1	0	0	1
Acinetobacter anitratum	1	0	0	1
Enterobacter cloacae	1	1	1	0
Staphylococcus albus	1	1	1	0

Twenty-three patients (68.8%) improved after 10-21 days of ampicillin or penicillin plus an aminoglycoside. One patient, whose isolate, P. aeruginosa was resistant to all drugs tested except the quinolones, was given ciprofloxacin for 21 days and likewise improved. The other patient with a ruptured nasoethmoidal meningocoele improved after 14 days of oxacillin and amikacin. Ten patients (31.2%) died within the first 24-48 hours of hospital stay. In six of these patients the following etiologic agents were identified: Klebsiella (2), E. coli (1), E. cloacae (1), Salmonella B (1) and S. albus (1).

DISCUSSION

Bacterial meningitis is the most common the first month of life more than any age group.[5, 8, 9] This could be explained partly by the fact that many neonatal host defence mechanisms have been shown to be abnormal and contribute to the increased susceptibility of these infants to bacterial infection. In this study, 11% of patients with neonatal sepsis had meningitis, much lower than the 20-30% incidence reported earlier in England and the U.S.[7, 10] Although this finding is more consistent with lower rates in more recent reports,[11] we believe that there is a considerable degree of underreporting occurring.

Because signs of neonatal meningitis may be very subtle and because clinical examination cannot distinguish septicemic newborns with co-existing meningitis from those without, early diagnosis through analysis of the CSF obtained by lumbar puncture deserves a high priority. The risks of lumbar puncture are minimal compared to the information gleaned by the procedure, the results of which direct the choice of antibiotic treatment and its duration.[12] In the event that the patient's initial condition is poor, a bacteriologic diagnosis may rest on blood cultures but a lumbar puncture should still be done when judged prudent. If this is not possible, then the child should be treated as if the meningitis were present. Empiric treatment for neonatal meningitis should cover for both gram-positive cocci as well a gram negative bacilli.

In this series, only 18.8% of patients manifested with complications. This is lower than other reports where complications were seen in 23-49%.[3, 5, 7, 12] Vigilant parent education with special emphasis on the need for closer follow-up and a multidisciplinary approach cannot be overemphasized.

Contrary to an earlier local report, GBS was found to be the most common gram-positive causative organism in the neonatal period and similar to reports in Thailand, Europe and the USA, the enteric gram negative bacilli are important agents, outnumbering the gram positive cocci. In the Philippines, as in other developing nations, Listeria monocytogenes has not been reported as an etiologic agent of neonatal meningitis.[5]

Unless one is considering enterococcus, Listeria or penicillin-resistant streptococci as an etiologic agent, in the local setting, Penicillin and an aminoglycoside is still the most cost-effective empiric treatment of neonatal meningitis. Other than its wider coverage which includes Listeria, ampicillin has no added advantage over penicillin. Adding a 3rd generation cephalosporin to penicillin would be a good alternative to penicillin and an aminoglycoside. The use of 3rd generation cephalosporins has gained wide popularity in the U.S. and Europe because of the anticipated problems with the use of aminoglycosides including the emergence of resistant gram-negative enteric bacilli, the adverse effects and the less adequate activity aminoglycosides in the CSF.[13, 14] Also, the 3rd generation cephalosporins have

extraordinary activity against common meningeal pathogens, are safe and rapidly sterilize the CSF. However, one must also keep in mind that routine use of cephalosporins in the hospital could lead to selection of resistant strains among the gram-negative enteric bacilli.[15]

BIBLIOGRAPHY

1. Lipton JD, Schafermeyer RW: Evolving Concepts in Pediatric Bacterial Meningitis - Part I: Pathophysiology and Diagnosis. Ann Emerg Med 1993; 22: 1602-15.
2. Shattuck KE, Chonmaitree T: The Changing Spectrum of Neonatal Meningitis Over a Fifteen-Year Period. Clinical Pediatrics 1992; 130-136.
3. Francis BM, Gilbert GL: Survey of Neonatal Meningitis in Australia: 19987-1980. Med J Aust 1992; 156: 240-43.
4. de Louvois J: Acute Bacterial Meningitis in the Newborn. J Antimicrob Chemo 1994; 34, Suppl A: 61-73.
5. Chotpitayasunongh T: Bacterial Meningitis in Children: Etiology and Clinical Features, An 11-Year Review of 618 Cases. Southeast Asian J Trop Med Public Health 1994; 25: 107-15.
6. Santana RT, Lansan MA, et al.: Clinical and Laboratory Profile of Bacterial Meningitis in Filipinos: A Six-Year Review. J Trop Geog Neurol 1992; 2: 151-6
7. Hristeva L, Booy R, et al.: Prospective Surveillance of Neonatal Meningitis. Arch Dis Child 1993; 69: 14-18.
8. Fortnum HM, Davis AC.: Epidemiology of Bacterial Meningitis. Arch Dis Child 1993; 68: 763-7.
9. Synnott MB, Morse DL, Jall SM: Neonatal Meningitis in England and Wales: A Review of Routine National Data. Arch Dis Child 1994; 71: F75-F80.
10. Klein JD, Feigin RD, McCracken GH, Jr.: Report on the Task Force on Diagnosis and Management of Meningitis. Pediatrics 1986; 78(suppl): 959-82.
11. Philip AG: The Changing Face of Neonatal Infection: Experience at a Regional Medical Center. Pediatr Infect Dis J 1994; 13: 1098-102.
12 Unhanand M, Mustafa MM, McCracken GH, Nelson JD: Gram-negative Enteric Bacillary Meningitis: A Twenty-One-Year Experience. J Pediatr 1993; 122: 15-21.
13. Lipton JD, Schafermeyer RW: Evolving Concepts of Pediatric Bacterial Meningitis - Part II: Current Management and Therapeutic Research. Ann Emerg Med 1993; 22: 1616-29.
14. Pohl CA, duPont Al: Practical Approach to Bacterial Meningitis in Childhood. Am Family Phys 1993; 47: 1595-1603.
15. McCracken GH: Current Management of Bacterial Meningitis in Infants and Children. Pediatr Infect Dis J 1992; 11: 169-74.