

ETIOLOGY AND NEUROLOGICAL COMPLICATIONS OF BACTERIAL MENINGITIS IN 189 PATIENTS

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Abstract — Results of a seven year (April 1985 to March 1992) prospective study of bacterial meningitis in 189 infants and children admitted to our Center indicate that: 1) The Gram-negative bacilli, especially *Klebsiella* species, are the leading cause of bacterial meningitis in neonates and young infants (<2 months), group B *Streptococcus meningitis* is rare, and *Listeria monocytogenes meningitis* is not observed. 2) *Haemophilus influenzae* is the leading cause of bacterial meningitis in children under 4 years old and *Streptococcus pneumoniae* becomes the leading cause over 5 years old. 3) Nine percent of *H. influenzae* isolates were ampicillin - resistant and 5% of *S. pneumoniae* were penicillin G resistant. All but one *Neisseria meningitidis* isolates were penicillin - susceptible. Both penicillin G / chloramphenicol or ampicillin/chloramphenicol resistance among these isolates were 2 percent. 4) The neurological complications and mortality were highest under two months of age, 39% of these neonates died due to complications as compared to 22% in all other age groups combined. 5) Dexamethasone improves outcome when used as an adjunctive therapy for bacterial meningitis in infants and children. The immediate and long-term clinical profiles both indicate better outcomes for dexamethasone.

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Key words: Bacterial meningitis; etiological agents; empirical therapy; dexamethasone; neurological complications

INTRODUCTION

Purulent bacterial meningitis is a life-threatening disease of children, often requiring initial of antimicrobials before the etiologic agent has been identified. Initial empirical antimicrobial selection requires knowledge of the expected infectious agents in a particular age group and their probable antimicrobial susceptibilities. Current recommendations suggest that in children of 3 months or less, the antimicrobial therapy is directed at group B *Streptococcus*, enteric Gram negative bacilli and *Listeria monocytogenes*, i.e. ampicillin plus an aminoglycoside or ampicillin plus cefotaxime (1,2,3). In children older than three months, since the most common causes of meningitis are *Haemophilus influenzae* types B, *Streptococcus pneumoniae* and *Neisseria meningitidis*, cefotaxime or ceftriaxone, plus vancomycin is recommended as the initial empirical therapy (4). In addition to antimicrobial therapy, several studies have shown benefit from the early institution of corticosteroid therapy in children with bacterial meningitis (5-8). This prospective study was

conducted in neonates and young children with meningitis is an effort to determine the antimicrobial susceptibilities of the organisms which were preponderant in different age groups. This study was designed to evaluate the use of dexamethasone administered in conjunction with antimicrobial chemotherapy in the treatment of meningitis in children.

MATERIALS AND METHODS

During seven years, from April 1985 to March 1992, 280 Patients were referred to our Center with the diagnosis of bacterial meningitis. Based on the positive results from the laboratory of bacteriology including blood and cerebrospinal fluid (CSF) cultures, Gram-stain of CSF, CSF latex agglutination tests for bacterial antigens, and other laboratory tests such as CSF cell count, CSF glucose and protein, complete blood count, erythrocyte sedimentation rate, serum glucose, electrolytes and calcium. Bacterial meningitis was defined by: abnormal CSF (i.e. increased protein, decreased glucose, increased neutrophil counts) and one or more positive results from culture, latex agglutination of Gram-stain. 91 Cases of 280 Patients in which the result of Gram-stain, latex agglutination, and culture were negative, as might have occurred in partially treated meningitis, were excluded from the analysis.

Patients and Treatment

On admission of the patients, history and physical examination were performed, and administered an empirical therapy based on the age: ampicillin plus an aminoglycoside for children less than two months. Older patients were randomly divided in two groups: (1) treated with antibiotics plus IV dexamethasone (0.15 mg/kg/6h) for 4 days and (2) treated with antibiotics alone. Antibiotics consisted of ampicillin or penicillin G in combination with chloramphenicol and dexamethasone for patients aged 61 days to 4 years, and penicillin and chloramphenicol combined with dexamethasone for children older than 5 years of age (group 1). Group 2 received the same antibiotics for initial therapy until the

organism's sensitivity was determined. We hospitalized patients for 1-6 weeks. During hospitalization patients were examined daily and one month, 5 months, and one year after discharged.

Laboratory Finding In CSF

Increased protein greater than 170 mg/dl in full-term is considered abnormal (9). Values less than 40 mg/dl are considered normal (10). CFS glucose level less than half of simultaneously obtained blood glucose concentration usually is considered abnormal (3). In neonates cell counts more than $8/\text{mm}^3$ with greater than 2/3 polymorphonuclear leukocytes is considered abnormal (10). By one month at age cell counts more than $6 \text{ cell}/\text{mm}^3$ with polymorphonuclear predominance are considered abnormal (10,11). Gram stained smear were performed for detecting bacteria. Latex-Particle agglutination tests (Biomeriex) of CSF were usually performed for detecting the polysaccharide antigens of H. Influenzae type B, S. Pneumoniae, (group A and C) Neisseria meningitidis and group B streptococci (10). All specimens of cerebrospinal fluid were routinely cultured on blood and chocolate agar plates and in thioglycolate broth and EMB agar (Eosine methylene blue). The disk diffusion susceptibility method was utilized to determine the antibiotic susceptibility patterns of the isolates.

Radiologic Evaluation

In some cases when fever persisted for at least seven days or when there were focal neurologic abnormalities computerized axial tomography (CAT scan) of the brain was performed.

Evaluation Of Hearing

In audiometric studies the hearing was assessed

within four weeks of hospital discharge by means of either brain stem auditory evoked responses or age appropriate behavioral measures (appropriate behavior measures are: behavioral responses, play audiometry, tympanometry, evoked response audiometry). The hearing test was selected according to the child's ability to cooperate. Audiometric studies were performed for patients able to do it outside hospital.

Statistical Analysis

Differences in the frequencies of various findings for both groups were tested with either the Chi-square test or Fischer's exact test. Only P values < 0.05 were considered significant.

RESULTS

Etiology: There were 189 well-documented cases of bacterial meningitis at our hospital. Of 189 patients included in the final analysis, there were 121 males and 68 females (Table 1). The results were analysed in group according to age. Gram-negative bacilli (GNB) were leading causes (32 cases) followed by N. meningitidis and S. pneumoniae (11 cases). One case of Staphylococcus aureus, one coagulase negative - staphylococcus and one group B streptococci (GBS) were identified within this group. There were 146 cases under four years of age, with H. influenzae being the leading cause (42, 146) followed by S. pneumoniae (n=36), Gram-negative bacilli (n=35), and N. meningitidis (n=26), Bacillus anthracis (n=1), staphylococcus aureus (n=1), enterococcus species (n=1) and peptostreptococcus species (n=1).

Table 1. Etiologic agents of meningitis in 189 children from birth to 12 years

Agents	Number of cases (%)				Total
	< 2 months	0-4 years	5-9 years	10-12 years	
S. pneumoniae	6 (13)	36 (25)	10 (40)	9 (50)	55 (29)
H. influenzae type B	2 (4)	42 (29)	1 (4)	1 (6)	44 (23)
N. meningitidis	5 (11)	26 (18)	12 (48)	6 (33)	44 (23)
Klebsiella species	10 (22)	13 (9)	0 (0)	0 (0)	13 (7)
Salmonella species	8 (18)	8 (5)	0 (0)	0 (0)	13 (7)
E. Coli species	8 (18)	8 (5)	0 (0)	0 (0)	8 (4)
Proteus species	1 (2)	1 (1)	0 (0)	1 (6)	2 (1)
Enterobacter species	2 (4)	2 (1)	0 (0)	0 (0)	2 (1)
Pseudomonas species	0 (0)	1 (1)	0 (0)	0 (0)	1 (0.5)
Serratia species	9 (0)	0 (0)	9 (0)	1 (6)	1 (0.5)
Staphylococcus aureus	1 (2)	2 (1)	1 (4)	0 (0)	3 (2)
Coagulase-negative Staphylococcus	1 (2)	1 (1)	0 (0)	0 (0)	1 (0.5)
Group B streptococcus	1 (2)	1 (2)	0 (0)	0 (0)	1 (0.5)
Enterococcus species	0 (0)	1 (1)	0 (0)	0 (0)	1 (0.5)
Flavobacter species	1 (2)	1 (1)	0 (0)	0 (0)	1 (0.5)
Total	46	146	25	18	189

Between 5-9 years the leading cause was *N. meningitidis* (12 cases), followed by *S. pneumoniae* (10 cases), *H. Influenzae* (1 case), *Bacillus anthracis* (1 case) and *Staphylococcus aureus* (1 case).

The *N. meningitidis* isolates from all age groups were either group A or C. The incidence of meningitis varies according to season. *H. influenzae* meningitis occurs chiefly in spring and autumn rather than summer and winter (29 cases vs 15 cases respectively). *N. meningitidis* however, prefers the warmer temperature of spring and summer, and the attack rates are 50% higher than they are fall and winter (29 cases vs 15 cases). In our experiments cases *S. pneumoniae* meningitis were seen in fall, winter and spring.

Laboratory Findings

Peripheral leukocyte counts obtained at the time of diagnosis varied widely, the mean leukocyte count was 10500/mm³ in all groups. Neutrophil and band-form counts varied from zero to 80% and from zero to 55% respectively. Platelet counts < 100000/mm³ were observed in 19% of patients in all groups. The SR was > 45 mm/h in 90% of patients (less than 25 mm/h is considered normal). The CSF glucose concentration ranged from zero to 85 mg/dl, and the CSF protein concentration ranged from 15-1800 mg/dl. In 65% of patients less than 2 months of age (46 patients) and older the CSF protein values were > 180 mg/dl and > 95 mg/dl respectively at diagnosis. Eight percent of all the patients had a CSF glucose concentration < 50 mg/dl and 67% of patients had CSF glucose concentration < 50 mg/dl and 67% of patients had CSF to blood glucose concentration ratio of less than 0.5.

Gram-stained smears of CSF revealed Gram-negative bacilli in 56% of those with a positive CSF culture under 2 months of age.

In 143 patients over two months of age the following results were obtained. Of 49 *S. pneumoniae* cases there were 22 cases with positive CSF culture 25 were just latex-positive, and 2 had positive blood and CSF culture with positive latex and Gram-stained smear. Of 42 cases due to *H. influenzae* type B there were 19 positive CSF cultures, 20 with only positive latex; 3 patients had positive blood and CSF culture with a positive latex and Gram-stained smear. Of 39 cases due to *N. meningitidis* 16 CSF cultures were positive, 19 were just latex-positive, and in the remaining 4 patients only the Gram-stained smears were positive with clinical manifestations. Other cases were diagnosed by CSF culture and Gram-stained smear.

Antimicrobial Susceptibility

Nine percent of *H. influenzae* isolated were ampicillin-resistant, however, all but one (with resistance to chloramphenicol and ampicillin) isolates were chloramphenicol susceptible. Five percent of *S.*

pneumoniae isolates were penicillin - resistant, however all but one (with resistance to both chloramphenicol and penicillin) isolates were chloramphenicol - susceptible. All but one of *N. meningitidis* isolated were penicillin and chloramphenicol - susceptible. One isolate was resistant to both penicillin and chloramphenicol.

Dexamethasone Treatment

Our results show that the hearing assessment in the dexamethasone treated group 1 and the non-treated group 2, from nine of the 28 (25%) evaluated cases presented with hearing loss, three (33%, 3/9) were treated with dexamethasone and six (67%, 6/9) were not. The number of cases were low due to shortage of audiometric facilities in our hospital.

It appeared that subdural empyema associated with *S. pneumoniae* meningitis developed in one case (without dexamethasone) (P=0.49).

Subdural effusion developed in 3 of 72 patients who were given dexamethasone and 12 of 71 patients who received antibiotic alone (P=0.01).

Seizures developed after 48 hours of treatment in 3 of 72 patients who were received dexamethasone and in 8 of 71 patients didn't received dexamethasone (P=0.11).

Cortical atrophy, ventricular dilatation or both, and cerebral infarcts identified on CT scanning were present in 6 of the patients in the dexamethasone group and 16 of the other group (Table 2) (P=0.02).

Long-term Responses To Therapy

Excluding the 31 patients who died, the 56 dexamethasone treated patients were followed for 12 months and the 56 patients given antibiotic only for 12 months, 44 patients in the dexamethasone group and 44 patients in the other group were available for one year after being discharged. There had been significantly higher percentage of patients with neurologic sequelae such as ataxia, hemiparesis and cranial nerve abnormalities in the group who received antibiotic only (Table 3) (P = 0.005).

There were few patients with meningitis caused by other pathogens to assess the effects of steroid treatment adequately.

Complications

The children under 2 months of age had the highest rate of neurological complications and mortality. Of the 46 infants in this age group, 18 (39%) died due to complications as compared to 31 of 143 (22%) in all the other age groups. Acute complications included ventriculitis in 22% of them. The diagnosis of ventriculitis was made by cranial computed tomography. Subdural empyema developed in one patient with *S. pneumoniae*. Subdural effusion occurred in 15% of infants, brain abscess occurred in 2 cases, 1 caused by

E.coli and 1 caused by Klebsiella. Among the survivors, 17 of 22 patients had permanent neurologic sequelae and 5 (23%) were physically normal on follow-up. Six patients who were not followed in our clinic or had underlying problems were not included in long term clinical evaluations.

Neurologic Sequelae

Hydrocephaly developed in 7 (31%) of 22 patients, a seizure disorder developed in 9 (40%) of 22 patients and long term anticonvulsant therapy was required. Of 22 patients, 8 (36%) acquired permanent spastic paralysis, 5 (22%) had severe mental and neurologic damage requiring constant care, 10 (45%) patients had development delay, and 61% of them had severe mental

retardation. In 5 patients, hearing deficit was documented.

The frequency of selected neurological findings and complications or sequelae in children above 2 months of age shown in (Tables 2,3 and 4). It is apparent from this data that the patients with pneumococcal meningitis suffered more frequently from focal neurologic signs, subdural empyema and sequelae than patients with H. influenzae or N. meningitidis.

17 of 49 patients due to S. pneumoniae, 6 of 42 patients due to H. influenzae and 4 of 39 patients due to N. meningitidis died. The frequency of neurological complications and sequelae by other pathogens were high.

Table 2. Characteristics of the study according to causal agent and complications or adverse events during treatment, according to treatment group.

Causal agent	Dexamethasone	No Dexamethasone	P value
	(N=72)	(N=71)	
	n (%)	n (%)	
H. Influenzae type B	21 (29)	21 (30)	
S. pneumoniae	24 (33)	25 (35)	
N. Meningitidis	20 (3=28)	19 (27)	
Others*	7 (10)	6 (8)	
Complication or Event			
Death at 72h.	15 (20)	16 (22)	p = 0.80
Subdural effusion	3 (4)	12 (17)	p = 0.01
Subdural empyema	0 (0)	1 (1)	p = 0.49
Onset of seizures 48h after start of therapy	3 (4)	8 (11)	p = 0.11
Abnormal cranial CT scan**	6 (8)	16 (23)	p = 0.02

* Klebsiella Species (3 P), Bacillus Anthracis (2), Brucella Species (1) Staphylococcus aureus (2) Seratia Species (1), Pseudomonas species (1) Proteus species (1) Enterococcus Species (1), and peptostreptococcus species (1). ** Abnormal findings were as follows: cortical atrophy, ventricular dilation or both, 6 patients in the dexamethasone group and 12 in the without dexamethasone group; cerebral infarct 4 patients in the without dexamethasone group.

Table 3. Neurologic outcome in the study patients evaluated up to one year after discharge, according to treatment group

Finding	Dexamethasone	No Dexamethasone	p value
	n (%)	n (%)	
Neurologic Sequelae			
No Evalutead	44	44	
Any abnormality	5 (11) ^{a,c}	21 (47) ^{b,c}	0.005
Excluding patients with Chronic Seizures			

a. Persistent mild ataxia (2), sever quadriparesis (1) and hydrocephalus (2).

b. The abnormalities observed were persistent, moderate ataxia (9), moderate hemiparesis (6), mild hemiparesis (2), severe paresis (2) and hydrocephalus (2).

c. The four patients (in two groups) who had persistent ataxia also had hearing loss.

Table 4. Characteristics of the study accrodng to causal agent and sequelae

	Group 1*	Group 2*	p value
	n(n)	n(n)	
	Living with sequelae	Living with sequelae	
H. Influenzae	13 (0)	14 (7)	p = 0.005
S. pneumoniae	13 (0)	15 (9)	p = 0.0008
N. Meningitidis	14 (2)	12 (2)	p = 1
Others***	4 (3)	3 (3)	p = 1

* Treated with dexamethasone and antibiotics; ** Treated with antibiotics only; *** Other organism's caused meningitis.

DISCUSSION

The most striking finding in this report is the apparent difference between the leading etiological agent of neonatal and young infants meningitis in developed countries and our hospital. Group B Streptococci is the most common cause of meningitis in children 2-6 weeks of age followed by *E.coli* and *Listeria monocytogenes* in many developed countries (4).

According to our studies, however, the GNB still seems to be the leading cause of meningitis among infants less than two months, moreover the leading cause is *Klebsiella* species among these bacilli as opposed to *E.coli* in developed countries (12-14).

Salmonella species also frequently cause meningitis in this group. The mortality rate of GNB meningitis is high (12-14). In contrast to developed countries *Listeria* and GBS did not seem to cause meningitis in babies under two months of age. Our studies show that, there was only one case of GBS meningitis in 1992 in a 50 day old child. *Listeria* was not isolated during the seven year duration of this study. This is probably due to the fact that GBS and *Listeria* are not often part of the normal flora of the vaginal tract of Iranian females.

In our other studies only 5 percent of Iranian pregnant women had vaginal colonization with group B Streptococci (unpublished data).

N. meningitidis and *S. pneumoniae* were isolated from patients in all ages, but most commonly from children older than 5 years of age. *H. influenzae* type B was not isolated from infants under one month.

Nine percent (4.44) of the *H. influenzae* and 5% (3.55) of *S. pneumoniae* isolated were ampicillin or penicillin resistant respectively. This is consistent with the finding of other investigators (15-18). Two percent of *H. influenzae* and *S. pneumoniae* isolates were resistant to both chloramphenicol and ampicillin or chloramphenicol and penicillin respectively. Chloramphenicol resistant *H. influenzae* have been reported previously (19). Two percent of *N meningitidis* isolates were resistant to both chloramphenicol and penicillin.

Penicillin resistant, *N. meningitidis* have been reported previously (20-21) however to our knowledge this is the first time *N. meningitidis* resistant to chloramphenicol is reported. Based on these data and due to the fact that the third generation cephalosporin or vancomycin are not always available, the following empirical antimicrobial regimens are recommended in cases of suspected meningitis in a particular age group: for neonates and young infants less than 2 months of age, ampicillin and gentamicin; for older children to 4 years, ampicillin and chloramphenicol, for children older than 5 years, penicillin and chloramphenicol, for initial therapy until organism's sensitivity has been determined (22-24).

Dexamethasone has been shown to bring about

significant reduction in cerebrospinal pressure, brain edema, and lactate concentration in cerebrospinal fluid in *S. pneumoniae*, *H. influenzae* meningitis and to decrease leakage of low-molecular-weight proteins from serum into the cerebrospinal fluid in the evolution of meningeal inflammation, dexamethasone was chosen as adjunctive therapy in infants and children with meningitis in an attempt to reduce the inflammatory response in the cerebrospinal fluid and to improve long-term outcome (2-8,24-28).

Lebel et al. found a significant reduction in the CSF leukocytes and an increase in glucose content 24 hours after initiation of antibiotic and steroid therapy (5). We did not detect these changes. This is because most of our patients were usually treated before hospitalization. We were not able to measure concentrations of interleukin-1 β , prostaglandin E2 and TNF - α and lumbar cerebrospinal pressure in the patients because it was not possible for us, follow-up neurologic and audiologic examinations were performed up to 1 year after the illness. Neurologic sequelae occur significantly more often in the patients who were given only antibiotics.

The higher rates of neurologic abnormalities and mortality in our patients are unexplained but may be a result of genetic or cultural differences or of the relative lack of newer antibiotics, advanced technological support systems and medical personnel in the intensive care unit.

Although the number of patients evaluated for hearing are low, it appears that dexamethasone therapy reduced hearing loss and accelerated the recovery rate. The difference is not significant in this study. This lack of statistical significance could be due to a sample that was too small for identifying a real difference.

Our study will continue and we may be able to report a significant difference later. This study suggests that dexamethasone treatment improves outcome by reducing the incidence of neurologic sequelae in *H. influenzae* and *S. pneumoniae* meningitis. We could not demonstrate, a reduced case fatality rate as Egypt and France studies (6,28).

The pathogenesis of sensorineural hearing loss due to bacterial meningitis involves the development of labyrinthitis. Bacteria can directly invade the cochlea hematogenously via the stria vascularis or through the cochlear aqueduct, which provides a pathway between the CSF and perilymph. Sensory elements of the cochlea are destroyed by the labyrinthitis. Ossification of the cochlea may develop and this appears to be more extensive after meningitis due to *Streptococcus pneumoniae* than that due to *H. influenzae* type B. Extensive ossification complicates the placement and perhaps diminishes, the performance of a cochlear implant. Bacteria may also reach the cochlea via the internal auditory canal in association with inflammation of the eighth cranial nerve. (29)

The sequelae of bacterial meningitis in many patients improve with time and may resolve completely. (30)

In conclusion we believe dexamethasone should be considered for treatment of patients with bacterial meningitis.

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