Disease burden and case management of bacterial meningitis among children under 5 years of age in Saudi Arabia

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ABSTRACT

Objectives: This study was designed to explore the case management and disease burden of bacterial meningitis among children below the age of 5 years in the Kingdom of Saudi Arabia.

Methods: A prospective descriptive study was conducted during June 1999 through to May 2001 in 8 hospitals from 5 cities in different areas of the country. Those were, King Fahad Specialist Hospital and Maternity & Children Hospital, Buraidah, Belgorashi General Hospital and King Fahad Specialist Hospital, Al-Baha, Maternity & Children Hospital and Ohud Hospital, Al-Madina, Al-Qatif General Hospital in the Eastern Region and Prince Abdulrahman Bin Ahmed Alsudairy Central Hospital, Sakaka. The study population was 171,818 children under the age of 5 years.

Results: During the study period 208 cases of bacterial meningitis were identified, 141 (67.8%) with a definite causative organism: *Hemophilus influenzae* type b, *Neisseria meningitidis, Streptococcus pneumoniae* and other bacterial species. The remaining 67 cases (32%) were labeled as aseptic meningitis. A considerable proportion of cases was found to have received an antibiotic prior to presentation. While symptoms such as fever or poor feeding were common among cases, meningeal signs were less prominent. A lumbar puncture was carried out on all cases to reach diagnosis by gram stain, latex agglutination test and cerebrospinal fluid (CSF) and blood cultures following standard procedures. The immediate burden of meningitis cases was found to be the lengthy stay of patients in the hospital wards and intensive care units. Some of the main causative agents were resistant to the conventional antimicrobial therapy, but susceptible to newer antibiotics.

Conclusion: The study being based on a population based surveillance gave a better overview on causative organisms of meningitis emphasizing that Gram stain, serology of CSF and culture (of CSF and blood) should be used. A high index of suspicion is needed to diagnose meningitis in children. Lumbar tap should be encouraged and supported in terms of training and more authorization to apply in diagnostic tests of such conditions. Audiometric measurement is a crucial need in the assessment of meningitis cases and in the process of their follow up. This type of service is clearly missing in our system. Influential steps are to be planned to avail this service.

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Meningitis can be caused by a wide variety of infectious agents, but in the potentially lethal form of the disease, the villains are bacteria. Acute bacterial meningitis was and is still a serious disease worldwide. The bacterial infection develops rapidly into a severe clinical illness, which may end fatally. Prior to the antibiotics era the death toll of this infection mounted to more than 70% of the diseased.

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The use of antibiotics has reduced this rate to less than 25% at the present time. Bacterial meningitis is dreaded not only as it kills, but also due to the possible long lasting neurological disabilities it causes such as hearing impairment, mental retardation, hydrocephalus and convulsions.[1,2] Despite the notable advances achieved in the fields of antimicrobial therapy, prophylaxis and vaccines, bacterial meningitis continues to be a major cause of morbidity, neurological complications and mortality.[3] Although bacterial meningitis is not solely a disease of childhood, it is a severe childhood illness, and most of its victims are infants and children. The 3 most common meningeal pathogens among children under the age of 5 years are *Hemophilus influenzae (H.influenzae)* type b, *Neisseria meningitidis (N.meningitidis)* and *Streptococcus pneumoniae (S.pneumoniae)*.[4,5] The prevalence of these organisms varies from region to region, and it also differs according to age and climatic conditions.[6,7] The risk of death and severe neurological disabilities following bacterial meningitis in childhood compounded with subtlety of its clinical signs render this disease a serious medical emergency which necessitates vigilance with regard to correct early diagnosis and prompt appropriate treatment.[3] Baraff et al[8] in their meta-analysis of bacterial meningitis outcomes in children found that 4.5% died and at least one major adverse outcome (severe intellectual disability, epilepsy, spasticity, deafness) was present in 16.4% of survivors. Due to the seriousness of the disease, antimicrobial therapy is usually administered empirically before the laboratory results are available.[9] Knowledge of the susceptibility patterns of the most frequent isolates will help in prescribing the initial therapy.

Methods. A national population based study on the epidemiological factors related to bacterial meningitis among children under 5 years of age in the Kingdom of Saudi Arabia (KSA), was conducted during the period from June 1999 through to May 2001. The study was carried out in hospitals with pediatrics services of 5 cities representing the different health regions of KSA. Those were; King Fahad Specialist Hospital and Maternity & Children Hospital in Buraidah, Belgorashi General Hospital and King Fahad Specialist Hospital in Al-Baha, Maternity & Children Hospital and Ohud Hospital in Al-Madina, Al-Qatif General Hospital in the Eastern Region and Prince Abdulrahman Bin Ahmed Alsudairy Hospital, Sakaka. The World health Organization guidelines protocol for *H.influenzae* type b population based survey was adopted in designing the study for the purpose of meaningful comparison to other countries.[10] This paper presents the clinical picture, microbiological laboratory findings and the disease burden. The study population in the 5 regions was 171,818 children under the age of 5 years. Cases were clinically suspected of having bacterial meningitis based on a set of case definitions; suspected case (an under 5-year-old child with clinical symptoms of meningitis); probable case. (meningitis symptoms with turbid cerebrospinal fluid (CSF) or CSF with elevated proteins >100 mg/dl, decreased glucose <40mg/dl, or leukocytosis >100 white blood cells/mm^3 with more than 80% neutrophils) and confirmed case (meningitis symptoms and detection of causative agent in the CSF). On admission relevant information was obtained including age, sex, duration of symptoms, antibiotics taken before admission. Following standard procedures, CSF collected by lumbar puncture (LP) for Gram staining, latex agglutination test (LAT), culture; and for cytology, protein and sugar examinations. Blood collected on admission from each patient for culture. Cerebrospinal fluid specimen centrifuged: the supernatant used for LAT to detect bacterial antigens, using Wellcogen Bacterial Antigen Kit, Murex Diagnostics Limited, England. This kit uses the rapid qualitative technique to detect specific polysaccharide surface antigens for *H.infleunzae* type b (Hib), *S.pneumoniae, Escherichia coli (E.coli)* K1, streptococcus group B and *N.meningitidis* groups A, B, C, Y and W135 antigens. The sediment utilized for Gram staining and culture on chocolate and blood agars following standard techniques. The isolates identified and their antimicrobial susceptibility determined by the disk diffusion technique of Kirby and Bauer; Ten antibiotic discs were used; *Staphylococcus aureus* (ATCC 25923) and *E.coli* (ATCC 2592) were used as control strains for Gram positive organisms and Gram negative organisms. Quality indicators were used to monitor both surveillance and laboratory activities. Data on meningitis cases were collected from all 5 regions during the study period. Data were reviewed twice before entry and was analyzed using Epi info version 6, a computer database and statistical program for epidemiology.[11] Categorical data were tested using X^2 test and Kruskall-Wallis; the non-parametric test was applied for continuous data.

Results. A total of 208 bacterial meningitis cases were identified within the 5 areas during the study period. The main presenting symptoms were fever, 197 (95%), refusal of feeds, 153 (74%) and irritability or both 136 (65%). Mean temperature was 38.7°C. Meningeal signs (neck stiffness, bulging fontanel, Kerning's sign and Brudzniski's sign) were of moderate occurrence as they were observed in 64 (30.7%), 48 (23%), 37 (17.8%) and 20 (9.6%) cases. Convulsions affected 60 cases (28.8%). Nine cases (4.3%) presented in coma and one case with septic shock. Sixteen cases (7.7%) had an underlying or associated condition: namely, hydrocephalus (6 cases), meningomyelocele (3), head trauma (2), and one each

Table 1 - Demographic distribution of meningitis cases according to type.

Type	Cases n (%)	Age (in months)*	Sex distribution M (n)	F (n)	M:F ratio
Hib	58 (27.8)	12.2 (6,8,13)	35	23	1.5:1
MCM	37 (17.8)	21.4 (9,18,30)	23	14	1.6:1
SPN	23 (11)	15 (3,6,12)	9	14	0.6:1
OTH	23 (11)	5.9 (1,1,10)	13	10	1.3:1
ASM	67 (32.2)	15.5 (1,6,20)	37	30	1.2:1
All cases	208 (100)	14.5 (3,8,20)	117	91	1.3:1
		$p<0.001$			

Hib - *hemophilus influenzae type b*, MCM - *Neisseria meningitidis*,
SPN - streptococcus *pneumoniae*, OTH - other bacterial species, ASM, aseptic meningitis,
M - male, F - female, n - number
Figures refer to mean (25th percentile, median, 75th percentile)

Table 2 - Meningitis cases cerebrospinal fluid (CSF) serology, culture and blood culture results.

Diagnosis	CSF Serology +ve/n (%)	CSF Culture +ve/n (%)	Blood culture +ve/n (%)
Hib	51/57 (89)	41/57 (72)	31/51 (61)
MCM (37)	31/36 (86)	30/36 (83)	14/34 (41)
SPN (23)	16/22 (73)	19/22 (86)	12/19 (63)
OTH (23)	5/23 (22)	20/23 (87)	9/10 (90)
Total	**103/138 (75)**	**110/138 (80)**	**66/114 (58)**
ASM (67)	0/67 (0)	0/67 (0)	0/40 (0)

Hib - *Hemophilus influenzae* type b, MCM - *Neisseria meningitidis*,
SPN - *streptococcus pneumoniae*, OTH - other bacterial species,
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with congenital heart disease, chromosomal anomaly, cerebral palsy, epilepsy and nephrotic syndrome. Only 13 (6%) cases presented with skin rash mainly petechial and purpural. The sex distribution was studied; the male to female ratio ranged 0.6-1.6:1 with an average ratio of 1.3:1 (**Table 1**). Prior to presentation to hospital, slightly less than half of the cases, 85 (41%) received an antibiotic, which was unidentified in 32 (37.6%) cases. The most commonly used antibiotic was amoxicillin (28%), then cefotaxime (12%), augmentin (7.1%), ampicillin (4.7%), vancomycin (3.5%), erythromycin (3.5%) cephradine (2.4%) and trimethoprim-sulphamethoxazole (1.2%). Lumbar puncture was performed on 205 (98.5%) cases, but not carried out on 3 due either to inability to obtain consent or unstability of the patient. Etiological organisms were identified by gram stain, LAT and CSF and blood cultures. A total of 141 (67.8%) cases were identified with a definite causative agent. Among these *H.influenzae* type b (Hib) was the predominant organism 58 (27.8%), followed by *N.meningitidis* 37 (17.8%) and *S. pneumoniae* 23 (11.0%). Other bacteria (OTH), namely *staphylococcus sp, streptococcus* group B, α-hemolytic streptococcus, *E.coli, klebsiella sp, salmonella sp*. and *candida sp*., were found in 23 (11%) cases. The remaining 67 (32.2%) cases were

Table 3 - Hospital and intensive care unit (ICU) stay according to diagnosis.

Type	Hospital stay (in days*)	Total days of stay	Stay in ICU (in days*)	Total stay of days
Hib	14.6 (10,12,16)	**645**	5.0 (3,4,7)	**75**
MCM	10.3 (8,10,12)	**361**	5.0 (5,5,5)	**10**
SPN	14.2 (10,14,17)	**326**	8.8 (4,8,10)	**88**
OTH	16.2 (10,11,15)	**339**	14.8 (6,7,14)	**163**
ASM	10.3 (7,10,12)	**575**	5.3 (2,5,8)	**80**
All cases	12.5 (9,11,14)	**2246**	7.8 (3,5,8)	**416**
	$p<0.001$		$p=0.0.96$	

Hib - *hemophilus influenzae type b*, MCM - *Neisseria meningitidis*,
SPN - streptococcus *pneumoniae*, OTH - other bacterial species, ASM, aseptic meningitis,
Figures refer to mean (25th percentile, median, 75th percentile)

Table 4 - Anti-microbial susceptibility of *hemophilus influenzae* (Hib) and *streptococcus pneumoniae* (SPN) isolates.

Hib isolates	Resistant n (%)	SPN isolates	Resistant n (%)
Antibiotic (n)		***Antibiotic (n)***	
Ampicillin (40)	8 (20)	Penicillin (20)	8 (40)
Chloramphenicol (40)	10 (25)	Chloramphenicol (20)	4 (20)
Ceftriaxone (40)	1 (2.5)	Ceftriaxone (20)	0 (0)
Cefuroxime (25)	2 (8)	Imipenem (11)	0 (0)

culture negative and no specific antigen detected; such cases were labeled as aseptic meningitis (ASM) (**Table 1**). Microscopic examination of gram-stained 205 CSF smears revealed the presence of 97 (47.3%) agents; of which 12.2% were gram positive organisms and 35.1% gram negative organisms. It showed no organism in 108 smears, of which 67 were aseptic cases (sensitivity of 80%, specificity of 100%). Latex agglutination test detected the antigens in 98 of 115 bacterial meningitis cases caused by the 3 main pathogens and was negative in all 67 aseptic cases tested (sensitivity 85.2% specificity 100%). Of 23 meningitis cases caused by OTH, LAT was positive only in 5 (22%) cases, all of which were *streptococcus* group B.

Culture of CSF was positive in 110 but negative in 28 bacterial meningitis cases, showing sensitivity of 80%. All 67 aseptic cases showed no growth (specificity of 100%). Blood culture was carried out in 114 of bacterial meningitis cases and in 40 aseptic meningitis (ASM) cases. The cultures were positive in 66 of the bacterial ones and negative in all aseptic cases (sensitivity 58%, specificity 100% (**Table 2**). There was an increase in the protein level, (mean 159 mg/dl) decrease in sugar level (mean 38.1 mg/dl) and polymorphonuclear predominance (67% of cases) in the majority of the CSF specimens. All cases were hospitalized for periods ranging from 2-67 days with a mean duration of stay of 12.5 days. Seventy-five percent of cases were treated as inpatients for 10 days or more. The duration was significantly shorter for N meningitidis cases ($p<0.001$) and longer for Hib cases ($p=0.03$). Nearly a quarter of cases, 53 cases (25.4%) needed admission to intensive care units (ICU) with a mean stay of 7.8 days and a total of 416 days of stay in ICU. There was no statistical difference in ICU duration of stay according to type of offending agent. ($p=0.096$) (**Table 3**). Neonates (aged <one month) constituted 30% of the cases admitted to ICU and exploited almost half of the total ICU stay; they were either cases of OTH or cases of ASM. Of 85 children (41%) who had received antibiotics prior to diagnosis: 30 had aseptic and 55 had bacterial meningitis. Gram stain showed organism in 34 of the 55 bacterial cases and was negative in 21 cases and in all aseptic cases (sensitivity 61.8%, specificity 100%). Latex agglutination test was positive in 45 and negative in 10

Table 5 - The outcome of meningitis cases according to type.

Outcome	Hib	MCM	SPN	OTH	ASM	Total n (%)
Discharged well	49	36	17	21	65	**188 (90.3)**
Discharged with disability	7	1	4	1	2	**15 (7.3)**
Died	2	0	2	1	0	**5 (2.4)**
Total	**58**	**37**	**23**	**23**	**67**	**208 (100)**

Hib - *hemophilus influenzae type b*, MCM - *Neisseria meningitidis*,
SPN - streptococcus *pneumoniae*, OTH - other bacterial species, ASM, aseptic meningitis,

bacterial cases. It was negative in all aseptic cases (sensitivity 81.8%, specificity 100%). Cerebrospinal fluid culture and blood culture had sensitivity of 75.5% and 66.6%. The specificity of each of them was 100%. Among the ASM cases there was no significant difference between those who received antibiotics and those who did not (28 versus 37, *p* value=0.78). **Table 4** shows the antimicrobial susceptibility pattern of Hib and *S.pneumoniae* isolates. The majority of isolates was sensitive to ceftriaxone, cefuroxime, augmentin, imipenem and least sensitive to penicillin, ampicillin and chloramphenicol. *Neisseria meningitidis* isolates were highly susceptible to the antibiotics tested. The vast majority of cases 188 (90.3%) was treated and discharged in good condition. Disability was detected in 15 (7.3%) patients: 6 with neurological sequelae, 5 with hearing impairment and 4 with arthritis. Hearing was assessed clinically (without audiometer) in 132 cases only. Eleven (73.3%) of the disabilities recorded among children aged 0-12 months ($p>0.45$). Five cases died during the study period giving a case fatality rate of 2.4%. Four (80%) of those who died were less than on year of age (**Table 5**).

Discussion. The majority of meningitis cases were found in children less than one year (134 cases, 64%). There was a higher attack rate among male children rather than females (male to female average ratio of 1.3:1) (**Table 1**). The age and sex distributions of cases in this study were consistent with previous reports.[4,12] Patients with acute bacterial meningitis classically present with fever, headache, meningismus and signs of cerebral dysfunction. These symptoms are found in more than 85% of patients.[13,14] However, young children and in particular neonates may not manifest many of the classical symptoms and signs of bacterial meningitis.[15] In accordance with this in our study where most of the cases (82%) were aged less than 2 years, the meningeal signs were not easy to elicit; and the most common symptoms were fever (90%), refusal to feed (74%) and irritability (65%), or both. The absence of the cardinal signs in neonates and infants patients necessitates a high index of suspicion to diagnose meningitis. Rutter and Smales suggested that in those children presenting with their first febrile convulsion under the age of 18 months LP is the only useful routine investigation.[16] Greenlee[17] stated that CSF evaluation is the single most important aspect of the laboratory diagnosis of meningitis. Despite such reports in favor of performing LP, its use in diagnosing meningitis in children is controversial.[18,19] In our study LP was the main tool for reaching a definitive diagnosis for the condition. It was performed in all but 3 of the 208 patients (98.5%). No cerebral herniation was reported and no death was related to the LP's. Microscopic examination of gram-stained, concentrated CSF was reported to be highly sensitive and specific in early diagnosis of bacterial meningitis.[20,21] In this study the gram-stained CSF smears correctly detected 80% of the cases, which correlates with the findings of other authors.[20,22,23] Bacterial antigens were detected in 85.2% of the cases by simple agglutination testing. Latex agglutination test was particularly sensitive in showing the main agents of childhood meningitis, such as *H.influenzae* type b, *N. meningitidis* and *S.pneumoniae*. From the other bacteria detected by CSF/blood cultures only streptococcus group B was identified by LAT (22%). Latex agglutination test could be positive only if the specific polysaccharide surface antigens of the organism were present in the commercial kit used. The Gram stain and LAT with their high detection rates aided in reaching an early presumptive identification of the likely causative agents before the results of the cultures were available. This is essential so as to administer an appropriate antimicrobial therapy as early as possible.[20,21] Before admission to hospital and LP performance, 55 of the bacterial meningitis patients had received some treatment with antibiotics. Our data indicated that the highest number of the causative agents in this group of patients, such 45 (81.8%) was detected by LAT; Gram-stained smears revealed organisms in 34 (61.8%) of these patients.

Cerebrospinal fluid culture and blood cultures were positive in 75.5% and 66.6%. In accordance with these findings Bhisitkul et al[24] reported that LAT should be performed whenever the patient had received prior antibiotic treatment. However, some studies do not recommend routine use of LAT in CSF analysis, but only in cases where gram stain fails to demonstrate an organism.[25,26] Other authors found that LAT offers no advantage in speed of diagnosis or in antibiotic pre-treated patients compared to routine Gram stain.[23,27] Furthermore, it has been noted that starting antibiotics prior to clinical sample collection decreased the detection of causative agents in bacterial meningitis by 30%.[28] Such a practice did not show a significant effect on identifying the etiological microorganisms in this study (p=0.78) (**Table 2**). *Hemophilus influenzae* type b isolates in this study showed an elevated resistance to conventional antibiotics; 20% were ampicillin resistant, 25% chloramphenicol resistant and 12% were resistant to both drugs. These findings were consistent with those of other investigators in KSA[29-31] and elsewhere in the world.[4,32-39] Ampicillin and chloramphenicol used to be the standard therapy for bacterial meningitis. Bacterial resistance emerged due to the production of and transferases against chloramphenicol β-lactamase and alteration of binding affinity of the penicillin binding proteins against ampicillin.[40] This has made it necessary to determine the susceptibility of clinical isolates routinely. Several studies have shown the high susceptibility of Hib to the third generation cephalosporins particularly cefotaxime or ceftriaxone.[38-43] In the present study ceftriaxone was used as empirical and standard treatment for all the cases. *Streptococcus pneumoniae* isolates showed an increasingly high resistance to penicillin mounting up to 40%, but were quite susceptible to ceftriaxone. There was no evident problem of drug resistance with *N.meningitidis* isolates. In addition to its broad bactericidal spectrum activity, ceftriaxone was found to penetrate into the CSF to achieve concentrations a hundred times higher than the minimal inhibitory concentrations of the main meningitis organisms.[44]

This study indicated that the immediate burden of acute meningitis on health services was the relatively long duration of case hospitalization. The mean hospital stay for all cases was 12.5 days, whereas it was 14.6 days for Hib patients. The long hospitalization in cases of Hib was also reported by other authors in South Africa[45] and Israel.[46] Furthermore, nearly a quarter (25.4%) of cases needed admission to the intensive care units (ICU). Neonates (aged <1 month) constituted 30% of these admissions. All neonates admitted to hospital were infected by OTH or ASM cases. Other authors have made similar observations.[47] The overall disability rate among the meningitis cases was 7.2%. Disability following Hib meningitis was 12% mostly neurological. Hearing impairment was detected in only 5 cases; 3 of them were due to Hib. These rates of hearing impairment, were much less than reported in other studies.[8,48-51] Based on an extensive review on Hib disease in Asia, Peltola assumed that the disability incidence not to be less than 30%.[52] Even in Northern Saudi Arabia such as Tabuk area, the major complications mounted to 14% among meningitis cases treated during a period of 5 years.[30] The prevalence of impaired hearing among the general population of Saudi Arabia was reported to be 2.6%, to which meningitis had a contribution of 8.9%.[53,54] However, the low incidence of hearing impairment detected among the patients in this study may be attributed to the lack of necessary equipment in the participating hospitals. The hearing assessment was performed clinically and only on 132 (64%) cases. The overall mortality rate was 2.4%; and 3.4% among the Hib cases. These figures are within the range of fatality rates of developed countries,[32,55] but lower than those rates (12-47%) reported from some developing counties[56] or the estimated 25% for Asia.[52] Previous hospital based studies in KSA yielded case fatality rates ranging from 2.8-14%.[57-59] However, the low prevalence of disability and decreased mortality rates may be due to the awareness of the emergency physicians during this study leading to an early recognition of the meningitis syndrome and instituting prompt treatment using an appropriate bactericidal antibiotic such as ceftriaxone.

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