Acute bacterial meningitis in Qatar

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ABSTRACT

Objectives: To study the changes in the epidemiology, clinical and bacteriological profiles of bacterial meningitis in the era of the *Haemophilus influenzae* type b (Hib)vaccine and pneumococcus resistance.

Methods: This is a retrospective study of children aged <12 years admitted to the Hamad Medical Corporation, Qatar between January 1998 through December 2002 with positive cerebrospinal fluid culture.

Results: We described 64 patients with culture proven bacterial meningitis. In infants <3 months (n=29 [45%]), the most common organism was Group B Streptococcus (GBS) (20%). Children >3 months (n=35 [55%]); Hib (25%) and *Streptococcus pneumoniae* (STP) (20%) were the most common organisms before introduction of Hib vaccination. A significant drop of Hib infections were noticed after introduction of the vaccine. Fever, neck stiffness, seizure, vomiting, and bulging fontanel were the most frequent presenting features. Group B Streptococcus were sensitive to ampicillin and cefotaxime with no resistance detected. Forty percent of STP isolates were resistant to penicillin and 12% were resistant to ceftriaxone. Fifty percent of Hib were resistant to ampicillin; while none of Hib were resistant to ceftriaxone. No case of *Listeria monocytogenes* meningitis was diagnosed. Morbidity was 28%, and one patient expired (2%) after *Klebsiella pneumoniae* meningitis. *Streptococcus pneumoniae* was associated with the highest morbidity (62%) while Hib had zero morbidity in our patients.

Conclusions: Bacterial meningitis is a serious illness with a significant morbidity and mortality. *Haemophilus influenzae* type b infection decreased which indicated an effective vaccination. As there is 12% bacterial resistance of STP reported against ceftriaxone; We recommend Cefotaxime for infants <3 months while ceftriaxone plus vancomycin as empiric therapy for older patients with community acquired bacterial meningitis. A pneumococcal vaccination may further decrease the incidence of meningitis in our community. A continuos surveillance to detect changes in the microbiology of organisms causing bacterial meningitis or their sensitivity in our community is essential to update these recommendations.

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Bacterial meningitis remains a very important disease worldwide. From its original recognition in 1805 until the early 1900s, bacterial meningitis was virtually 100% fatal.[1] According to a World Health Organization estimate, approximately 171,000 people worldwide die from bacterial meningitis each year. Even with antimicrobial treatment, fatality rates are as high as 5-10% in the developed world.[2] The incidence and mortality rates are much higher in third-world countries.[2] Between 10% and 20% of those who do survive bacterial meningitis suffer permanent damage such as mental retardation, deafness, or epilepsy.[3] Adding to the tragedy is the fact that these deaths could have been avoided; either through vaccination or by accurate diagnosis and rapid intervention. The most common organisms

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causing bacterial meningitis have varied according to the population studied. In small infants the most common infections are *Group B Streptococcus* (GBS) and gram-negative organisms. While *Haemophilus influenzae* type b *(Hib), Streptococcus pneumoniae* (STP), and *Neisseria meningitidis* (NSM) were the most common organisms causing disease in older age groups in pre-vaccination era.[4] Newly introduced vaccines against STP, Hib and NSM proved to effective as it reduced the incidence of meningitis.[4] Recently the resistance to new antibiotics is increasing.[5,6] Clinicians typically initiate therapy for meningitis empirically before the etiologic agent is confirmed, the decreased incidence of meningitis vaccinated organisms and the increase in antimicrobial resistance among pneumococci had influenced the choices for empirical treatment of meningitis.[1,5,6] Data defining the frequency of isolation of specific pathogens, their antibiotic sensitivities, and the associated morbidity and mortality are changing every few years. Accordingly, the continuous evaluation of the epidemiology of bacterial meningitis has an important implication for both public health planning and clinical management.[1,5,6] This, and the recent introduction of *Hib* and pneumococcal vaccinations in Qatar, has prompted us to review all cases of bacterial meningitis that were admitted to our hospital over 5 years period in attempt to ascertain these data, and to plan our management of these cases in the future.

Methods. A retrospective chart review was conducted to all patients aged <12 years who were diagnosed with acute bacterial meningitis from January 1998 through December 2002 at Hamad Medical Corporation, a large public hospital, and the only hospital providing acute medical care in Qatar. Patients were identified using the computerized medical filling system, obligatory notifications to health authorities and the microbiology laboratory records. Informations collected included age, gender, nationality, presenting complaints, clinical findings on admission, associated illness, laboratory data, treatment, and outcome. Only patients (<12 years) with the compatible clinical picture plus a positive cerebrospinal fluid (CSF) culture were included. Patients who had abnormal CSF, but a negative culture were excluded. Patients were grouped accordingly into 4 age groups (<3 months, 3-24, 24-60, 60-144 months). Symptoms at presentation were divided into 4 groups (fever alone, fever with signs of increased intracranial pressure without seizures, fever with seizures without signs of increased intracranial pressure and change of level of consciousness alone). Sensitivity and resistance data were considered against empirically used antibiotics in its specific age groups (Ampicillin and Cefotaxime in small infants; and Vancomycin and ceftriaxone in older age groups). Morbidity was classified into groups (deafness, hydrocephalus, epilepsy, paralysis, and mental retardation). Collections of data from medical records were carried out by one investigator and rechecked through another investigator through computerized bacteriology laboratory results to avoid missing data and bias. After coding, all data were introduced by another investigator. Meningitis was considered nosocomial if the diagnosis was made after a minimum of 7 days after hospitalization, with initial hospitalization unrelated to meningitis or sepsis; or the patient underwent surgery within the previous 4 weeks.

Hospital laboratory recommendations and protocol for meningitis work out. Lumbar puncture was carried out under aseptic condition and CSF was immediately sent to the laboratory for analysis. Gram's staining and latex agglutination tests were carried out by Wellcogen Bacterial Antigen kits for the detection of antigen from *Hib, STP*, *NSM*, *GBS*, and *Escherichia coli K1*. A portion of the CSF was cultured for bacteria by direct inoculation into chocolate, blood and MacConkey agar, as well as subculture in brain heart broth. Antibiotic susceptibilities were determined by minimum inhibitory concentration (MIC) using the VITEK 2 system. Minimum inhibitory concentration results were interpreted according to the National Communities of Clinical Laborites Standards (NCCLS), which recommended a considerable sensitivity of ceftriaxone <0.5 MIC and <2 for STP and Hib. Minimum inhibitory concentration of ceftriaxone >2 are considered resistance for both organisms. Another portion of the CSF was used for cytology, estimation of glucose, and protein. Other investigations carried out included complete blood counts, blood sugar, and blood culture.

Results. A total of 64 patients met the study criteria for the diagnosis of bacterial meningitis. The mean age was 14 months (range 7 days-7 years). The most common age was infants <3 months, followed by infants between 3-24 months (**Table 1**). The male to female ratio was 1.2:1. The overall incidence was 10 per 100,000 age group (<12 years). **Table 1** lists the age specific rates per 100, 000 population. Ten patients (16%) were diagnosed in 1998, 19 patients (30%) in 1999 and 10 (10%) patients in 2000, 16 patients (25%) in 2001 and 9 (14%) patients in 2002 (**Table 2**). Meningitis was a community acquired bacteria in 94% patients and 6% nosocomial in the remaining 3 patients. The clinical features was listed in **Figure 1**. The fever was the most common presenting

Table 1 - Causative pathogen in relation to different age groups.

Age (months)	n	(%)	Incidence 10\100000	STP	Hib	NSM	GBS	GM⁺ve*	GM⁻ve†
<3	29	(45)	214	1	3	1	6	8	10
4-24	17	(27)	17	3	5	2	0	4	3
25-60	15	(23)	9	3	4	0	0	6	2
60-144	3	(5)	0.8	1	0	1	0	1	0
Total	**64**	**(100)**		**8**	**12**	**4**	**6**	**19**	**15**

*Gram positive organism (*Staphylococci epidermidis, Staphylococcus haemolyticus, Streptococcus sanigous, Streptococcus viridans*),
†Gram negative organism (*Klebsillae pneumoniae, Pseudomonas aerogenosa, Salmonella, Acinetobacter junii, Flavobacterium meningosepticum*),
STP - *Streptococcus pneumoniae*, Hib - *Haemophilus influenzae* type b, NSM - *Neisseria meningitidis*, GBS - *group B Streptococcus*

Table 2 - Incidence of causative organisms/100,000 population.

Total causative incidence/10^5	1998 10 (8.4/10^5)	1999 19 (15/10^5)	2000 10 (6.3/10^5)	2001 16 (8.5/10^5)	2002 9 (6.7/10^5)
STP (1.3)	3 (2.5)	2 (1.6)	1 (0.8)	1 (0.8)	1 (0.7)
HIB (1.9)	1 (0.8)	8 (6.4)	0	2 (1.5)	1 (0.7)
NSM (0.6)	2 (1.7)	1 (0.8)	0	1 (0.8)	0
GBS (1.1)	0	3 (3.1)	2 (1.6)	1 (0.8)	0
GM⁻ ve (2.8)	2 (1.7)	1 (0.8)	3 (2.3)	5 (3.8)	4 (3)
GM⁺ ve (3)	2 (1.7)	4 (3.2)	4 (3.1)	6 (4.6)	3 (2.2)

STP - *Streptococcus pneumoniae*, Hib - *Haemophilus influenzae* type b, NSM - *Neisseria meningitidis*, GBS - *group B Streptococcus,*
GM⁺ ve - Gram positive organism, GM⁻ ve - Gram negative organism

feature occurring in 92% of patients, followed by neck stiffness or bulging fontanels noticed in 58%, seizures in 23% and change of level of consciousness alone in 8%. Main presentation in infants <3 months is fever with convulsions (50%) compared to (19%) infants more >3 months of age. Bulging fontanels was noticed in 64% of infants <3 months compared to (16%) infants >3 months. Clinical presentations in relation to different organisms are observed at **Figure 2**. *Group B Streptococcus* presented by seizures was 50%; while Hib presented by seizures in 27%, STP in 25% and NSM in 0%. Bulging fontanels or neck rigidity were noticed in 72% of patients with Hib, 75% with STP and 100% with NSM. The majority of patients had no predisposing factors for meningitis (94%); while others (6%) occurred with prior history of head injury.

Table 1 shows the causative organisms in different age groups. As GBS was the most common organism in small infants; the Hib was the most common organism in other age groups. The years (2000-2001) following Hib vaccination incidence dropped from (6.4/100,000 population year 1999) to (0.7/100,000 population year 2002). Forty percent of STP isolates were resistant to penicillin (MIC >2); and 12% were resistant to ceftriaxone (MIC >0.5). Fifty percent of Hib isolates were resistant to Ampicillin (MIC >4), and all were sensitive to ceftriaxone (MIC <2). *Neisseria meningitidis* isolates were sensitive to penicillin. GBS was sensitive to Penicillin and Ampicillin. Gram negatives were sensitive to ceftriaxone and 15% resistance against to Gentamycin. Gram positives were sensitive to Vancomycin (68%) and Cloxacillin (21%).

Table 3 and 4 show the cerebrospinal fluid analysis results. Gram stain was positive in 56% and ranges from 10-100% of patients according to the causative organism. The Latex antigen test was positive in 51%

patients and ranges from 67-88%. Out of 33 patients (48%) who had radiological studies either CT scan or MRI; 16 patients had abnormal neurological finding. Seven out of 8 (87%) STP meningitis associated with abnormal radiological finding compared to 2/4 (50%), 2/6 (33%) and 1/6 (16%) cases of *N. meningitidis*, Hib meningitis and GBS meningitis. Subdural effusions were the most common abnormality noticed 9/16 (56%); while 6/16 (38%) had hydrocephalus and 5/16 (31%) had brain edema. Treatment was started empirically according to different age groups and possible causative organisms. Cefotaxime and Ampicillin used for infants <3 months and Cefotaxime or Ceftriaxone used alone until 2002 and along with Vancomycin when first resistance reported in STP. Steroids were used routinely in all pediatric patients with suspected Hib meningitis. The outcome in relation to causative organisms is shown in **Table 5**. Neurological complications developed in 14/49 patients (28%) (15 patients missing follow up), 10/49 (20%) had epilepsy, 6/49 (12%) motor disability, 5/49 (10%) mental retardation, 2 (4%) deafness and 3/49 (6%) hydrocephalus. Fifty-eight percent (4/19) of infants <3 months acquired complications compared to 10/30 (33%) of older ages. Eight patients out of 18 (44%) who presented with signs of increased intracranial pressure obtained neurological complications compared to 6/31 (19%). One patient died post *K. pneumoniae* meningitis after 3 days of treatment of Ceftriaxone and Amikacin. It was resistant to Ceftriaxone and only sensitive to Imipenem.

Discussion. The present study was a continuity of our effort from our previous studies about meningitis.[7-9] Collection of data were carried out through our computerized medical system and obligatory notifications to the public health authorities to minimize possibility of missing cases. As our target is to update our information about causative bacterial organisms; only cases of cultured proven bacterial meningitis were included. Sixty-four patients of bacterial meningitis were identified during the study period. The overall annual incidence was 10/105. The mean age is 14 months which coincides with the decline in the passively acquired maternal antibodies. Only 5% of cases occurred in patients after the age of 5 years, while 45% of patients were <3 months; this figure will be much lower if we excluded maternally acquired infections in the neonatal period. The clinical features were similar in many aspects to those reported by others (**Figure 2**).[10] The majority of patients presented with fever, nuchal rigidity, bulging fontanels, and seizures. Small infants (<3

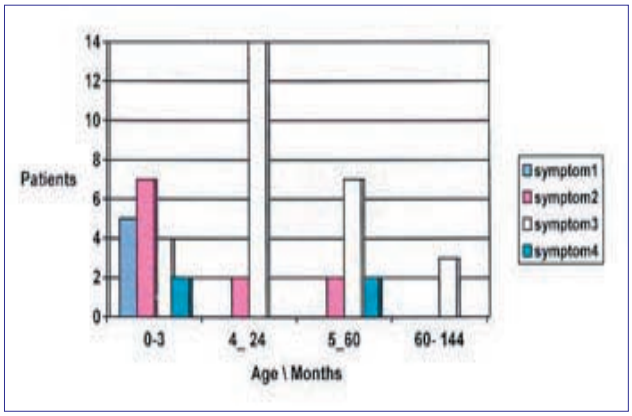

Figure 1 - Symptoms of meningitis in different age groups.

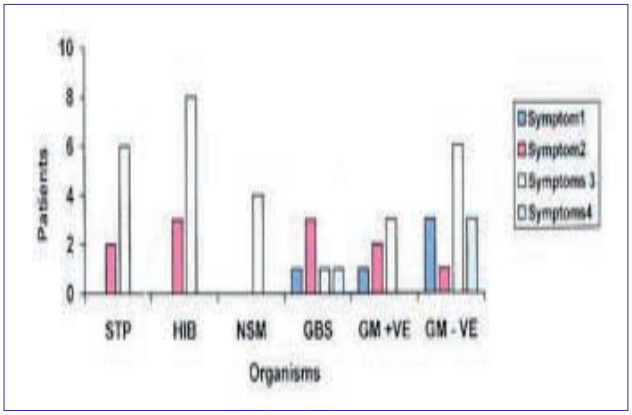

Figure 2 - Presentations of meningitis according to organisms. STP - *Streptococcus pneumoniae*, Hib - *Haemophilus influenzae* type b, NSM - *Neisseria meningitidis*, GBS - *group B Streptococcus,* GM^+ ve - Gram positive organism, GM^- ve - Gram negative organism

Table 3 - CSF analysis results for Gram stain and latex testing.

Test	Positive latex %	Positive gram stain %
STP	88	100
HIB	91	82
NSM	100	75
GBS	67	67
GM^-ve	NA	22
GM^+ve	NA	10

STP - *Streptococcus pneumoniae*, Hib - *Haemophilus influenzae* type b, NSM - *Neisseria meningitidis*, GBS - *group B Streptococcus,*
GBS-ve - Gram positive organism,
GM+ve - Gram negative organism,
NA - not applicable

Table 4 - Biochemical profile of cerebrospinal fluid (CSF).

Cytology and biochemistry	Maximum	Minimum
White blood cell	12000	4
Protein G/L	9.5	0.3
Glucose ratio (CSF/blood)	0.7	0

months) presented only with fever in 27% as lumbar puncture is routinely carried out for septic work. Seizures was observed in 23% of patients, similar to 10-29% reported in other studies.[10] Fifty percent of small infants presented with seizures compared to 19% in patients >3 months. This mostly due to subtle signs of meningitis in small infants which delay clinical presentations to the hospital. Seizures were noticed in 50% of GBS, 27% Hib and 25% of STP. Main presenting symptom of STP and Hib is bulging fontal or neck rigidity in 75% and 72% of cases. *Streptococcus pneumoniae* and Hib were the most common isolated organisms. The incidence of Hib in Qatar is reduced from 6.4/105 to 0.7/105 (90% reduction) after introduction of Hib vaccine in Qatar in September 2000 (**Table 2**). In the prevaccination area; the incidence of Hib ranges from 22/105 to 71/105 in USA and Europe.[11,12] Vaccine was effective in lowering the annual prevalence of Hib meningitis in well-immunized populations by 76-90%.[13] We think that the Prevenar vaccination will further reduce the incidence of pneumococcal meningitis in the country. As expected, GBS was observed exclusively in patients <3 months. *Haemophilus influenzae* type b was seen only in aged <5 years, while NSM and STP was distributed all over the age groups. The most striking findings of this study are the very low incidence of NSM, and the absence of *Listeria monocytogenes* as causes of meningitis. The absence of *Listeria monocytogenes* and *E. coli* as a cause of meningitis in our study cannot be explained. The low incidence of NSM could be partially explained by the fact that many people from Qatar visit Saudi Arabia frequently for Hajj and Omra and they are requested to have meningococcal vaccination before they are allowed to enter the country. Approximately 18,000 vaccinations are given yearly by the Preventive Health Department in the Ministry of Public Health of Qatar. Knowing that protection provided by the meningococcal vaccine continues for at least 2 years,[14] this means that a significant proportion of the population are protected from meningococcal disease, contributing to the low incidence of meningococcal meningitis in the country. The absence of *Listeria monocytogenes* as a cause of meningitis in our study reported in the previous local studies.[7-9] Another important finding in our study is the high incidence of penicillin resistance among our pneumococcal and Hib isolates reaching to 40 and 50%. Resistance to ceftriaxone was absent among Hib isolates while STP resistance (12%) noticed after the year 2000. The important therapeutic implication of these findings is that ceftriaxone with vancomycin as empiric therapy should be adequate initially. Isolation of Hib in children <3 months justifies usage of Cefotaxime; while absence of *Listeria monocytogenes* as a cause of bacterial meningitis in our community makes the addition of ampicillin to ceftriaxone in the initial antibiotic regimen in patients with no comorbid conditions unnecessary. *Klebsiella pneumoniae* which was resistant to amikacin and ceftriaxone; caused single mortality in a small infant <3 months. However, this high resistance frontally did not show up since 1998. Continuous surveillance for antibiotic resistance among our isolates is essential, as changes in their antibiotic sensitivities may result in a change in the recommendation for empiric antibiotic therapy. Cerebrospinal fluid bacterial antigen detection was

Table 5 - Complications of meningitis against age, organisms, symptoms.

Morbidity	Number (%)	
	Yes	No
Age (months)		
0-3	4 (21)	15 (79)
4-24	4 (25)	11 (75)
25-60	3 (27)	8 (73)
60-144	2 (66)	1 (36)
Organisms		
STP	5 (62)	3 (38)
HIB	0	11 (100)
NSM	1 (25)	3 (75)
GBS	1 (17)	5 (83)
GM−VE	3 (38)	5 (62)
GM+VE	4 (33)	8 (67)
Symptoms		
Symptoms 1	2 (50)	2 (50)
Symptoms 2	2 (18)	9 (82)
Symptoms 3	10 (55)	8 (45)
Symptoms 4	0	4 (100)

STP - *Streptococcus pneumoniae*, Hib - *Haemophilus influenzae* type b, NSM - *Neisseria meningitidis*, GBS - *group B Streptococcus,*
GM^+ ve - Gram positive organism,
GM^- ve - Gram negative organism,
NA - not applicable

frequently positive in our patients (50%). Others have quoted much lower rates.[15,16] The latex bacterial antigen detection and gram stain are a useful test in patients with bacterial meningitis specially in STP and NSM (up to 100%) (**Table 3**). However, a negative test does not rule out meningitis. There is a chance that the blood culture will yield the causative organism as has been demonstrated in our study (12%) and by others.[15] Although antibiotic delay has not been clearly established as an independent risk factor influencing clinical outcome,[1,18] it is generally accepted that early effective antibiotic therapy improves survival and decrease neurologic sequelae.[17-19] The mortality was observed in our series was 2%, although lower than that reported by others, it remains significant. The reason for this low mortality is probably related to the easy access to medical survival in the State of Qatar. Patients with Hib meningitis had no morbidity in our study, which may be due to the use of steroids in all these patients. Despite the advances in our intensive care units and management; our morbidity rate is high (28%) as previously reported in developed countries (18-27%).[17-20] Patients with pneumococcal meningitis had the highest morbidity (62%) (**Table 4**). This shows the importance of protecting our people against STP by more widespread use of the pneumococcal vaccine. However, PCV contains a limited number of pneumococcal serotypes (7 serotypes). Geographic serotypes have different distributions and even more serotypes are changing as has been demonstrated.[21,22] Only 50% of causative serotypes in infants <2 years with 2 invasive serotype (6b and 23f) were included in the Prevnar 7 valent vaccine (local survey in personal communication). So that, non-vaccine serotypes remains a threat. Therefore, monitoring disease burden and defining immune correlate of protection after widespread use of conjugate vaccines are crucial for the evaluation of these new generation vaccines. The conjugated vaccine (heptavalent) is recently introduced in Qatar at 2005; so its effectiveness against meningitis has to monitored in the next few years. Furthermore, a need exists to develop pneumococcal vaccines with larger serotype coverage.

In conclusion, bacterial meningitis continues to be a serious illness in our community with significant morbidity and mortality. *Streptococcus pneumoniae* is the most common pathogens causing meningitis in our community. The recent introduction of Hib vaccine in Qatar reduced effectively the incidence in the country. Inclusion of the conjugated pneumococcal vaccine as components of childhood vaccination may further reduces meningitis incidence in our community, therefore, continuous surveillance for organisms causing bacterial meningitis to monitor these changes and monitor antibiotic resistance among our isolates is essential.

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