Clinical presentation of acute bacterial meningitis in Qatar

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ABSTRACT

Objectives: To study the changes in the epidemiology of bacterial meningitis in the era of the *Hemophilus influenzae (H. influenzae)* type b vaccine and pneumoccous resistance.

Methods: Retrospective study which included patients admitted to Hamad Medical Corporation, Doha, Qatar between January 1998 through to December 2000 with positive cerebrospinal fluid culture.

Results: Thirty-seven patients with culture proven bacterial meningitis were described. *Streptococcus pneumoniae (S. pneumoniae)* and *H. influenzae* were the most common organisms, accounting for 30% and 24% of cases. Fever, neck stiffness, vomiting, and bulging fontanel were the most frequent presenting features. Fifty four percent of *S. pneumoniae* isolates were resistant to penicillin, and 22% of *H. influenzae* were resistant to ampicillin, but both were sensitive to ceftriaxone. No cases of *Listeria monocytogenes* meningitis were diagnosed. Morbidity was 32%, and mortality 5%. Poor outcome was associated with altered mental status on admission.

Conclusions: Bacterial meningitis is a serious illness in our community with significant morbidity and mortality. *Streptococcus pneumoniae* and *H. influenzae* are the most frequent pathogens causing meningitis in our community. As there is no bacterial resistance (*S. pneumoniae* and *H. influenzae*) reported against ceftrixone, we recommend ceftriaxone alone as empiric therapy for patients with no comorbid conditions presenting with community acquired bacterial meningitis. A continuous surveillance for 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 recognition in 1805 to the early 20th century, bacterial meningitis was fatal.[1] Although the introduction of antibiotics made it curable, morbidity and mortality from the disease remains unacceptably high.[1] The most common organisms causing bacterial meningitis have varied according to the population studied, however, until recently *Hemophilus influenzae (H. influenzae)*, *Streptococcus pneumoniae (S. pneumoniae)*, and *Neisseria meningitidis (N. meningitidis)* were the most common organisms causing this disease.[2] The introduction of *H. influenzae* type b vaccine in many developed countries caused almost elimination of *H. influenzae* as a cause of childhood meningitis in these countries.[3] Due to clinicians typically initiating therapy for meningitis before the etiologic agent is confirmed, the decrease in *H. influenzae* meningitis and the increase in antimicrobial resistance among *pneumococci* had influenced the choices for empirical treatment of meningitis.[1] Accordingly evaluation of the epidemiology of bacterial

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meningitis in the era of the *H. influenzae* type b vaccine and *pneumoccous* resistance has important implication for both public health planning and clinical management.[1] Data defining the frequency of isolation of specific meningeal pathogens in cases of bacterial meningitis, their antibiotic sensitivities, and the associated morbidity and mortality is lacking from this part of the world. This, and the recent introduction of *H. influenzae* type b vaccination in the country, has prompted us to review all cases of bacterial meningitis admitted to our hospital over a 3-year period in an attempt to ascertain this data, and to plan our management of future cases.

Methods. A retrospective chart review was conducted of all patients, one month of age or older, diagnosed with acute bacterial meningitis from January 1998 through to December 2000 at Hamad Medical Corporation (HMC), Doha, Qatar, a large public hospital, and the only hospital providing acute medical care in Qatar. Patients were identified using the medical filing system, and the microbiology laboratory records. Information collected included age, sex, nationality, presenting complaints, clinical findings on admission, associated illness, laboratory data, treatment, and outcome. Lumbar puncture was carried out under aseptic condition and cerebrospinal fluid (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 *H. influenzae* type b, *S. pneumoniae, N. meningitidis*, group B *Streptococcus (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 heart and brain broth. Antibiotic susceptibilities were determined by minimum inhibitory concentration (MIC) using the VITEK 2 system. Minimum inhibitory concentration results were interpreted according to national communities of clinical laboratries standards (NCCLS) which recommend a MIC of ceftriaxone <0.5 and <2 for *S.pneumoniae* and *H. influenzae* type b to be considered sensitive. Minimum inhibitory concentration of ceftriaxone >2 is considered resistance for both organism. Another portion of the CSF was used for cytology, estimation of glucose, and protein. Other investigations carried out included complete blood count, blood sugar, and blood culture. The diagnosis of bacterial meningitis was based on a compatible clinical picture plus a positive CSF culture. Patients who had abnormal CSF, but a negative culture were excluded. 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; the patient was hospitalized within the previous 14 days; or the patient underwent surgery within the previous 4 weeks.

Statistical analysis. All analysis was performed by use of the statistical package for social sciences (SPSS) software.

Results. A total of 37 patients met the study criteria for the diagnosis of bacterial meningitis. The mean age was 11 years (range 2 months-60 years) and the male:female ratio was 1.2:1. Fourteen patients were Qatari and 23 were expatriates. The overall incidence was 2.24 per 100 000. **Table 1** lists the age specific rates per 100,000 population. Eleven patients (30%) were diagnosed in 1998, 15 patients (40%) in 1999 and 11 (30%) patients in 2000. Meningitis was community acquired in 34 patients, and nosocomial in the remaining 3 patients.

Clinical features. **Table 2** lists the most common presenting features at the time of presentation. Fever was the most common presenting feature occurring in 94% of patients, followed by neck stiffness (71%), bulging fontanel in 8\13 children with open anterior fontanelle (61%), vomiting (56%), and seizures in (38%). The majority of patients had no predisposing factors for meningitis (76%). Five cases occurred in patients with prior history of head injury, 2 patients had ventriculo-peritoneal shunts, and 2 had malignant diseases. Associated illnesses in relation to different types of organisms are shown in **Table 3**.

Causative organisms. *Streptococcus pneumoniae* caused 11 (30%) of the 37 cases of meningitis, *H. influenzae* 9 (24%), and *N. meningitidis* 2 (5%). *Klebsiella pneumoniae, Salmonella species, Staphylococcus hemolyticus,* and *Streptococcus viridans* were responsible for 2 cases each. One case each was due to *Acinetobacter junii, Pseudomonas, Staphylococcus epidermis, Streptococcus sanginous, Staphylococcus hominus, GBS* and *Flavibacterium meningosepticum.* **Table 1** lists the causative organisms in relation to different age groups. Fifty-four percent of *S. pneumoniae* isolates were resistant to penicillin (MIC>2); however all were sensitive to ceftriaxone (MIC<0.5). Twenty-two percent of *H. influenzae* isolates were resistant to ampicillin (MIC>4), and all were sensitive to ceftriaxone (MIC<2). Both *N. meningitidis* isolates were sensitive to penicillin. Blood culture was positive in 21 patients (57%) showing the causative organism.

Cerebrospinal fluid analysis. Cerebrospinal fluid analysis results are shown in **Table 4**. Gram stain was positive in 22 patients (59%) showing the causative organism. Eight/nine (88%) of *hemophilus,* 10/11 (90%) of *S. pneumonia* and 2/2 of *N. meningitis* had positive results. Latex antigen test was positive in 19 (51%) patients. It was positive in 9 (80%) of patients with *S. pneumoniae* meningitis, 8 (89%) of *H. influenzae* and 2 (100%) of *N. meningitidis* meningitis. Latex test was negative in the patient with *GBS* meningitis.

Treatment. Treatment was started empirically

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

Age	Case /100,000	Total	*S. pneumoniae*	*H. influenzae*	*N. meningitidis*	Other gram negative *Bacilli**	Other gram positive *Cocci***	GBS
1-12 months	46.5	**13**	2	5	1	2	2	1
1-5 years	5	**13**	4	4	0	2	3	0
>5-15 years	1.3	**4**	3	0	1	0	0	0
>15 years	0.5	**7**	2	0	0	3	2	0
Total n (%)	**2.24**	**37**	**11 (30)**	**9 (24)**	**2 (5)**	**7 (19)**	**7 (19)**	**1 (3)**

* gram negative organism (*Klebsiella pneumoniae, pseudomonas aeruginosa, salmonella, acinetobacter junii, flavobacterium meningosepticum*)
** gram positive organism (*Staphylococcus epidermidis, staphylococcus hemolyticus, streptococcus sanigous, streptococcus viridans*)
GBS - Group B *streptococcus, S - streptococcus, H - hemophilus, N - neisseria,* n - number

Table 2 - Symptoms and signs compared to other studies.

Symptom/sign	Present study	Kilpi	Sigudardottir	Durand
Fever	94	85	92	95
Coma	7	7	11	6
Vomiting	56	59	NS	NS
Irritability	0	65	NS	NS
Neck stiffness	71	78	82	88
Focal neurological	7	7	NS	28
Bulging fontanel	61	NS	NS	NS
Seizures	38	19	10	29

NS - not stated

Table 3 - Past medical history in relation to the causative organism.

Past medical history	Normal n (%)	Head injury (%)	VP shunt n (%)	Malignancy n (%)
Streptococcus pneumoniae	9/11 (81)	(9)	1 (9)	0
HIB	8/9 (89)	(11)	0	0
Neisseria meningitidis	2/2 (100)		0	0
GBS	1/1 (100)		0	0
Other gram negative *bacilli*	4/7 (57)	(29)	1 (14)	0
Other gram positive *cocci*	4/7 (57)	(14)	0	2 (29)
Total	**28/37 (75.7)**	**(13.5)**	**2 (5.4)**	**2 (5.4)**

VP shunt - ventriculo-peritoneal shunts, *GBS* - group B *streptococcus*, HIB - *Hemophilus influenzae*, n - number

Table 4 - Cerebrospinal fluid findings in patients with bacterial meningitis.

CSF cytochemistery	Mean (range)	Standard deviation
Leukocytes (/mm)	987 (5-4310)	1398
Neutrophils (%)	(83)	13.4
Protein (gm/dl)	2.6 (0.17-27)	4.9
CSF sugar/blood sugar	0.2 (0.001-0.6)	0.1

CSF - cerebrospinal fluid

Table 5 - The outcome in relation to the causative organisms.

Organism	Morbidity n (%)	Mortality n (%)
S. pneumoniae	6/11 (54)	1/11 (9)
H. influenzae	0/9	0/9
GBS	0/1	0/1
N. meningitidis	0/2	0/2
Other gram negative *bacilli*	3/7 (42)	1/7 (14)
Other gram positive *cocci*	3/7 (42)	-
Total	**12/37 (32)**	**2/37 (5)**

S - *streptococcus*, H - *hemophilus*, *GBS* - group B *streptococcus*, *N - nisseria*, n - number

according to different age groups and possible causative organisms. Ceftriaxone used alone or combination with another antibiotics was the most commonly prescribed initial antibiotic in 29 (78%) patients. Steroids were used routinely in all pediatric patients with suspected *H. influenzae* meningitis.

Outcome. The outcome in relation to causative organisms is shown in **Table 5**. Thirty-five (95%) patients survived. Two patients (5%) died due to their illness. Neurologic complications developed in 9 patients. Nine patients (24%) had epilepsy, 7 (19%) motor disability, 5 (13.5%) mental retardation, 3 (8%) deafness and 2 (5%) hydrocephalus.

Discussion. The present study was an effort to collect data of all cases of culture proven bacterial meningitis that were admitted to HMC over a 3-year period. As HMC is the only hospital providing acute medical care in the state of Qatar, all medical inpatient filing system, and microbiology laboratory results are computerized; therefore we believe that the findings of this study reflects the actual number of cases of culture proven bacterial meningitis in Qatar during the study period. However, since cases of partially treated bacterial meningitis were excluded, the results of this study do not reflect the actual number of cases of bacterial meningitis in Qatar, hence the incidence figures reported in this study will be an underestimate of the actual incidence. The percentage of some pathogens such as meningococcal organism may be underestimated as *meningococcus* can be eradicated with orally used antibiotics. Other results, such as clinical presentation, complications, sensitivity and resistance of organism are reasonable. Thirty-seven patients with bacterial meningitis were identified during the study period. The overall annual incidence was 2.24 per 100,000. The peak attack rate occurred at 6-8 months of age, which coincides with the decline in the passively acquired maternal antibodies. More than two-thirds (69%) of cases occurred in patients under the age of 5 years, similar to figures from the developed countries before the introduction of *H. influenzae* vaccination in these countries.[4]

The clinical features were similar in many aspects to those reported by others **(Table 2)**.[5-7] The majority of patients presented with fever, nuchal rigidity, bulging fontanels, and seizures. The incidence of bulging fontanel in this series was high (61%), this could be explained by the fact that most of our patients were children less than one year of age. Seizures were observed in 38% of patients, higher than the rate of 10-29% reported in other studies.[8,9] *Streptococcus pneumoniae* and *H. influenzae* were the most common isolated organisms. Since mandatory vaccination of all children with the *H. influenzae* vaccine was started in Qatar in September 2000, the last year of the study, a significant effect on the incidence of *H. influenzae* meningitis was not expected. As expected *H. influenzae* was seen only in those under the age of 5-years, while *S. pneumoniae* was distributed throughout the age groups. The most striking findings of this study are the very low incidence of *N. meningitidis*, and the absence of *Listeria monocytogenes (L. monocytogenes)* as causes of meningitis. The low incidence of *N. meningitidis* could be partially explained by the fact that many people from Qatar visit the Kingdom of Saudi Arabia frequently for Hajj and Umra. 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, Qatar. Knowing that protection provided by the meningococcal vaccine continues for at least 2-years,[10] this means that a significant proportion of the population are protected from meningococcal disease, contributing to the low incidence of meninigococcal meningitis in the

country. *Listeria monocytogenes* has become the 4th leading cause of bacterial meningitis in the United States of America after the introduction of *H. influenzae* type b vaccine.[11] The absence of *L. monocytogenes* as a cause of meningitis in our study cannot be explained. Another important finding in our study is the high incidence of penicillin resistance among our *pneumococcal* isolates reaching 54%. Fortunately resistance to ceftriaxone was absent among these isolates. Among *H. influenzae* isolates ampicillin resistance was (22%); however, there was no resistance to ceftriaxone or cefotaxime. The important therapeutic implication of these findings is that penicillin or ampicillin are not suitable as empiric therapy for patients suspected to have bacterial meningitis in Qatar. As cefriaxone and cefotaxime have an excellent activity against *N. meningitidis*, either drug alone is adequate, and there is no need to include vancomycin in the initial antibiotic regimen at this stage. The absence of *L. 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. 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 frequently positive in our patients (50%). Others have quoted much lower rates.[12,13] It was particularly highly positive in patients with *S. pneumoniae*, (80%) *H. influenzae* (89%), *N. meningitidis* meningitis (100%). This indicates the latex bacterial antigen detection is a useful test in patients with bacterial meningitis, however, a negative test does not rule out meningitis, and the physician should depend on his clinical assessment, and other tests in cases of suspected bacterial meningitis. Bacterial meningitis is considered to be a medical emergency. Antibiotics should be started as early as possible, and should not be delayed until laboratory and radiological studies are performed.[14] Although antibiotic delay has not been clearly established as an independent risk factor influencing clinical outcome,[1,15] it is generally accepted that early effective antibiotic therapy improves survival and decreases neurologic sequelae.[16] In the event that there will an anticipated delay in doing these tests, blood cultures should be collected and antibiotics given. There is a good chance that the blood culture will yield the causative organism as has been demonstrated in our study and by others.[17]

The mortality observed in our series was 5%, 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 service in the State of Qatar. As the number of patients who died was small, no definite conclusion could be drawn regarding factors that are associated with poor outcome; nevertheless, the 2 patients who died in our series were comatosed on presentation, confirming other observations that an altered mental state or coma on presentation is associated with a poorer outcome.[16] Morbidity was especially high in patients with *pneumococcal* meningitis (54%). This demonstrates the importance of protecting our people against *S. pneumoniae* by more widespread use of the *pneumococcal* vaccine. Patients with *H. infuenzae* meningitis had no mortality or morbidity in our study, which may be due to the use of steroids in all of these patients.

In conclusion, bacterial meningitis continues to be a serious illness in our community with significant morbidity and mortality. *Streptococcus pneumoniae, H. influenzae,* and *N. meningitidis* are the most common pathogens causing meningitis in our community. However the recent introduction of *H. influenzae* tybe b vaccine in Qatar, and the anticipated inclusion of the conjugated *pneumococcal* vaccine in the near future as components of childhood vaccination, will result in a change in the epidemiology of pathogens causing meningitis in our community. Therefore continuous surveillance for organisms causing bacterial meningitis to monitor these changes and monitor antibiotic resistance among our isolates is essential education for physicians to the seriousness of the illness and the urgency to start treatment as early as possible which, is necessary to improve the outcome in our patients.

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