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BURDEN OF BACTERIAL MENINGITIS: A RETROSPECTIVE REVIEW ON LABORATORY PARAMETERS AND FACTORS ASSOCIATED WITH DEATH IN MENINGITIS, KELANTAN MALAYSIA

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ABSTRACT

To describe the clinical characteristics and the risk factors associated with mortality in patients with meningitis. This is a retrospective review of patients diagnosed to have meningitis with positive culture of the cerebrospinal fluid (CSF) specimen. All cases aged 19 > years who were admitted to Hospital USM between January 2004 and December 2011 were included in the study. The CSF results database were obtained from the Department of Medical Microbiology and Parasitology, Hospital USM, Kelantan. A checklist was used to record the clinical characteristics. A total of 125 cases met the inclusion criteria. The age of patients ranged between newborn and 19 years old (Mean±SD, 74.5±80.6 months). The majority of them were males (65.6%). Fever was the most common presentation (73.6%) followed by poor oral intake (48.0%), seizure (36.0%) and headache (24.8%). The mortality rate was 31.2%. Coagulase negative staphylococcus was the most frequent pathogens isolated (21.6%), followed by *Acinetobacter* spp. (17.6%), *Staphylococcus aureus* (13.6%), *Streptococcus* spp. (11.2%) and *Klebsiella pneumoniae* (6.4%). There were significant association of in-hospital death with age (p=0.020) and conscious level (p=0.001). Infectious meningitis is a big health concern, especially among children. We found that coagulase negative staphylococcus, *Acinetobacter* species, *S. aureus*, *Streptococcus* spp and *K. pneumoniae* were prevalent in our hospital. These microorganisms were hospital associated pathogens. The 31% mortality linked to hospital acquired meningitis specifies the need for focused physician attention especially among younger aged patients.

Key Words: Bacterial meningitis, children, CSF, Mortality

INTRODUCTION

Meningitis is a devastating and deadly disease that kills patients within hours. Despite many new antibacterial agents, bacterial meningitis fatality rates still remain high. It is the cause of

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mortality in about 1,000 people around the world every day; many of them children and young adults. Survivors can be left with severe disabilities.

Infectious meningitis could be typed on the bases of several markers. The markers include pathogen: bacterial, viral, fungal, or parasitic; and host age: neonatal, young or mature adult. Individual health status is also a marker which includes normal or deficient immunity, and symptoms duration: acute or chronic.

Pediatric bacterial meningitis is most common in children younger than four years, with a peak incidence in those aged 3–8 months. The most common bacterial causes of acute meningitis in young children are *Streptococcus agalactiae* and *Escherichia coli*. These bacterium commonly infect neonates and infants up to age three months and were acquired during birth when the infant passes through the vaginal canal.

What is known is that *Haemophilus influenzae* infects unvaccinated children between the age of 3–6 months and 6 years; *Neisseria meningitides* infects children and young adults[1)] and it is the only organism that causes meningitis epidemics.[2)] Evidence suggests that *Streptococcus pneumoniae* occasionally infects children and increases in incidence with age. *Listeria monocytogenes* appears to be food-borne (dairy products, processed meat, uncooked vegetables) and affected immunocompromised patients.[1)]

The early symptoms of meningitis are headache, fever, and chills.[3)] A combination of neck stiffness, seizure and altered mental status has also been found in bacterial meningitis patients. Shock, coagulation disorders, endocarditis, pyogenic arthritis, and prolonged fever are the most common bacterial meningitis complications.[1)] Death occurs from shock and other serious complications within hours of the appearance of symptoms.[3)] Among survivors, the outcomes of meningitis include deafness, mental retardation, spasticity and/or paresis, and seizure disorder.

Published studies on meningitis are very few in the Southeast Asian region. There were only 20 research articles that clinically evaluated meningitis over a period of ten years (1990–2000).[4)] Similarly, there has been very few studies on meningitis among Malaysian children or adolescents in the last two decades. Thus, we hope this study will add information to the existing data and fill in the gaps of information for the purpose of reducing mortality rates. The aim of this study was to describe the clinical features, laboratory profile and the mortality rate of meningitis among children and adolescent in our hospital setting.

METHODOLOGY

Hospital Universiti Sains Malaysia (Hospital USM) is a tertiary teaching hospital which receives referrals from several district hospitals in Kelantan. The Hospital is also a referral center for neurosurgery within East Coast Malaysia. This hospital has a 15-bed neurosurgical ICU and is one of the training hospitals for neurosurgical subspecialty in Malaysia.

This study is a retrospective review of patients diagnosed to have bacterial meningitis with positive culture of the cerebrospinal fluid (CSF) specimen. The CSF results database were obtained from the Department of Medical Microbiology and Parasitology, Hospital USM, Kelantan, Malaysia and patients' records were obtained from the record office of Hospital USM with permission. All cases aged 19 > years who were admitted to Hospital USM between January 2004 and December 2011 were included in the study. A checklist was used to record the clinical characteristics, accompanying symptoms and signs, results of relevant blood investigations and the patient's outcome.

CSF specimens received from the ward were processed according to the standard laboratory protocol adopted from the Clinical and Laboratory Standards Institute (CLSI). The gross ap-

pearances of the CSF specimens were recorded. Microscopic examination of the CSF specimens were performed which included total cell count, Gram staining and India ink preparation followed by culture and susceptibility testing. Latex agglutination examination for five primary pathogens namely *Streptococcus pneumoniae*, *Escherichia coli*, *Haemophillus influenzae*, *Neisseria meningitides* and group B streptococcus was performed using Wellcogen™ Bacterial Antigen Kit (Remel, United Kingdom). The CSF specimens were also analyzed biochemically for glucose, protein and globulin levels. In some cases, the plasma glucose was also taken at the time of lumbar puncture to determine the CSF/plasma glucose ratio.

The data were statistically analyzed using SPSS version 20 (Chicago, USA). Descriptive statistics, Mann-Whitney test and the Pearson chi-squared test were used to investigate different indicators of meningitis. P-values less than 0.05 were considered to be statistically significant.

RESULTS

We obtained a total of 141 CSF specimens for bacterial culture during the study period. The CSF specimens of 16 patients did not meet the laboratory diagnostic criteria. As such, 125 cases were included in the final analysis.

Table 1 shows the socio-demographic characteristics of the 125 cases. The age ranged from newborn to 19 years old, with 43.2% aged less than 1 year, 13.6% aged 1 to 5 and 43.2% aged above 5 years old. The mean (SD) age was 74.5 (80.6) months. The majority of cases were males (65.6%). In this study, patients originated from Terengganu (27%), Kota Bharu (28%), and other districts of Kelantan (37.6%).

The clinical presentations of the meningitis were also shown in Table 1. Fever was the most common presentation (73.6%) followed by poor oral intake (48.0%), seizure (36.0%) and headache (24.8%). It is noted here that headache was noted by those above five year olds. The incidence of postoperative nosocomial meningitis was 67% (84 patients out of 125 patients). The distribution of underlying diseases of the patients were: congenital hydrocephalus 43% (35 patients), motor vehicle accident 20% (16 patients), brain tumor 4% (four patients), hydrocephalus 29% (25 patients), brain abscess 2% (two patients), spine bifida 1% (one patient), and aterio venous malformation 1% (one patient).

Post-operative meningeal infection mainly EVD shunt infection; was highly significant as indicated by Pearson chi square test (.000). Out of 125 cases of meningitis between 2004 and 2011, 31.2% died while in hospital due to meningitis and its related complications. The remaining 33% was community acquired (41 patients out of 125 patients) survived as were determined as bacterial meningitis cases.

Table 2 shows results of CSF examinations. Positive latex agglutination test were seen in 6.4% cases. Further examinations showed 28% had clear CSF and the rest were either blood stain, cloudy, turbid or xanthochromic.

Total cell counts by microscopic examination revealed that the mean total white blood cells was 990.7 (2344.2) cells/mm^3. It was found that mean polymorph counts were higher than lymphocytes mean counts. TRBC was found to be a little elevated in CSF due to traumatic tap.

Microscopic examinations showed that 20 (16.0%) were Gram negative bacteria, 24 (19.2%) were Gram positive bacteria and 81 (64.8%) were undetermined. The microorganisms isolated from the CSF cultures in descending order were: coagulase negative staphylococcus (21.6%), *Acinetobacter* spp (17.6%), *Staphylococcus aureus* (13.6%), *Streptococcus* spp (11.2%) and *Klebsiella pneumoniae* (6.4 %). The mean (SD) of CSF protein was 47.34 (471.88) mmol/l and mean (SD) of CSF glucose was 1.40 (1.20) mmol/l.

Table 1 Socio-demographic characteristics, clinical presentation and outcome of patients with bacterial meningitis

	Frequency (%) n=125
Age	
>5–19 year	54 (43.2)
>one – 5 year	17 (13.6)
≤one year	54 (43.2)
Sex	
Male	82 (65.6)
Female	43 (34.4)
District	
Kota Bharu	35 (28.0)
Terengganu	34 (27.2)
Other districts	47 (37.6)
Missing	9 (7.2)
Diagnosis	
Congenital hydrocephalus	35 (43%)
Motor vehicle accident	16 (20%)
Brain tumor	4 (4%)
Hydrocephalus	25 (29%)
Brain abscess	2 (2%)
Spine bifida 1	1 (1%)
Aterio venous malformation	1 (1%)
Clinical features	
Fever	92 (73.6)
Poor oral intake	60 (48.0)
Seizure	45 (36.0)
Headache	31 (24.8)
Altered conscious level	19 (15.2)
Neck stiffness	19 (15.2)
Confusion	14 (11.2)
Blurred vision	14 (11.2)
Hydrocephalus	13 (10.4)
Bulging fontanelle	6 (4.8)
Pneumonia	5 (4.0)
Complication	
Nerve palsy	5 (4.0)
Paralyze	5 (4.0)
Increased muscle tone	4 (3.2)
Skin rashes	3 (2.4)
Diarrhea	3 (2.4)
Outcome	
Death	39 (31.2)
Alive	86 (68.8)

Table 2 Results of cerebrospinal fluid investigation of patients with bacterial meningitis

Cerebrospinal fluid	n	Frequency (%)	Mean (SD)	Median (IQR)
Latex agglutination	125			
Positive		8 (6.4)		
negative		117 (93.6)		
Cell count (cells/mm^3)				
TWBC	88			
Polymorph	83		990.7 (2344.2)	125 (772)
Leucocyte	57		922.9 (2303.7)	100 (823)
TRBC	73		185.1 (618.8)	34 (82)
			3857.2 (15348.0)	150 (1366)
Macroscopic appearance				
Clear		35 (28.0)		
Blood stain		25 (20.0)		
Cloudy		3 (2.4)		
Turbid		13 (10.4)		
Xanthochromic		14 (11.2)		
Aetiological agents				
Coagulase negative *staphylococcus*		27 (21.6)		
Acinetobacter species		22 (17.6)		
Staphylococcus aureus		17 (13.6)		
Streptococcus species		14 (11.2)		
Klebsiella pneumonia		8 (6.4)		
Others[#]		37 (29.6)		
Gram Stain				
Gram negative bacteria		20 (16.0)		
Gram positive bacteria		24 (19.2)		
No organism seen		81 (64.8)		
Positive India ink		0 (0.0)		
Biochemical test: Globulin				
Positive		46 (36.8)		
Negative		22 (17.6)		
Trace		3 (2.4)		
Not done		54 (43.2)		
Protein (g/dL)* [0.15–0.45]	113		47.34 (471.88)	
Glucose (mmol/L)* [2.2–4.4]	112		1.40 (1.20)	
CSF/Plasma glucose ratio*	48		0.29 (0.29)	

*skewed data

Based on our results, Positive Gram stain, high CSF WBC count, and high CSF protein count determines in bacterial meningitis. In this study 36% of patients were positive for globulin. It is mentioned here that CSF gamma globulin may help to determine the amount of protein in CSF. Increase in gamma protein level is a diagnostic criterion for neurological diseases.

From the hospital records, mortality from bacterial meningitis was 31.2% (39/125). Table 3 shows the associated factors for death from bacterial meningitis using Chi square test. There were significant associations between mortality with age (p=0.020) and conscious level (p=0.001). There were no significant associations between death and gender, fever, seizure, poor feeding, neck stiffness, headache, latex positive, level of CRP and level of protein, glucose and CSF/ plasma glucose ratio.

For logistic regression analysis, the independent variables of mortality were age and level of consciousness (GCS <10). Table 4 shows results of multiple logistic regressions between patients' age and conscious level. Infants with bacterial meningitis were significantly three times more vulnerable to risk of death compared to children older than five years (p=0.013). Patients who presented altered conscious levels had significantly five times more likely to die compared to those who were conscious.

Table 3 Factors associated with outcome of patients with bacterial meningitis

	Frequency (%)		P value
	Death N=39	Alive N=86	
Age			0.020[c]
≤ one year	11 (28.2)	43 (50.0)	
>one – 5 year	4 (10.3)	13 (15.1)	
>5–19 year	24 (61.5)	30 (34.9)	
Sex			0.812 [c]
Male	25 (64.1)	57 (66.3)	
Female	14 (35.9)	29 (33.7)	
Fever			0.897 [c]
Yes	29 (74.4)	63 (73.3)	
No	10 (25.6)	23 (26.4)	
Altered conscious level			0.001 [c]
Yes	12 (30.8)	7 (8.1)	
No	27 (69.2)	79 (91.9)	
Seizure			0.111 [c]
Yes	18 (46.2)	27 (31.4)	
No	21 (53.8)	59 (68.6)	
Poor feeding			0.781 [c]
Yes	18 (46.2)	42 (48.8)	
No	21 (53.8)	44 (51.2)	
Neck stiffness			0.618 [c]
Yes	5 (12.8)	14 (16.3)	
No	34 (87.2)	72 (83.7)	

Headache			0.053 [c]
Yes	14 (35.9)	17 (19.8)	
No	25 (64.1)	69 (80.2)	
Latex			1.000 [c]
Negative	37 (94.9)	80 (93.0)	
Positive	2 (5.1)	6 (7.0)	
CRP	114.5 (126.0)	69.5 (137.0)	0.165 [c]
CSF Protein[a] g/dl	1.25 (5.72)	1.56 (3.58)	0.752 [b]
CSF Glucose[a] (mmol/L)	1.00 (1.66)	1.15 (1.66)	0.479 [b]
CSF/Plasma glucose ratio[a]	0.22 (0.41)	0.21 (0.29)	0.412 [b]

[a]median (interquartile range)
[b]Mann Whitney test
[c]Chi square test

Table 4 Factors associated with mortality outcome of patients with bacterial meningitis by using binary multiple logistic regressions

	Crude OR (95% CI)	Adjusted OR (95% CI)	P value
Age			
>5–19 year	1.00	1.00	
>one – 5 year	2.60 (0.75, 9.01)	3.35 (0.87, 12.83)	0.078
≤ one year	3.13 (1.33, 7.34)	3.11 (1.28, 7.56)	0.013
Altered conscious level			
No	1.00	1.00	
Yes	5.02 (1.79, 14.04)	5.41 (1.82, 16.07)	0.002

OR = Odds Ratio
CI = Confidence Interval

DISCUSSION

A study done by Erleena Nur *et al.* (2008) found that the majority of bacterial meningitis admitted to a tertiary hospital in the West Coast of Malaysia were children less than five years old and the most common organisms were *S. pneumoniae* (23%), *H. influenzae* (15%), *E. coli* (8.5%), *N. meningitides* (4%) and *Streptococcus* spp (2%). Studies done before 1998 showed that Haemophilus influenzae type b (Hib) were the most common aetiological agent.[6,7] In comparison to our study, even though the most frequent age diagnosed with bacterial meningitis remained similar; the trend of microorganisms isolated differed. In this study, we found that coagulase negative staphylococcus, *Acinetobacter* species, *S. aureus*, *Streptococcus* spp and *K. pneumoniae* were prevalent in our hospital site according to their clinical background and underlying diseases of the patient. These microorganisms were hospital associated pathogens. Other authors had noted that Gram-negative bacteria, most commonly *Acinetobacter* spp and *P. aeruginosa*; have gained importance as hospital pathogens.[8-11]

This also explains why most of the latex agglutination gave negative results. Latex agglutination tests are mainly used to determine specific community acquired meningitis but not to

determine hospital acquired meningitis. The cases in our study were a mixture of hospital and community acquired meningitis which was expected as our hospital was the referral centre for neurosurgery. Most of the hospital acquired bacterial meningitis cases in our study were found in patients with congenital hydrocephalus who had undergone ventriculo-peritoneal shunt.

The clinical symptoms and signs of bacterial meningitis in children vary. It depends on the age of the child and duration of disease. Nonspecific signs include abnormal vital signs such as tachycardia and fever, poor feeding, irritability, lethargy, and vomiting.[12] Classical signs of meningitis include nuchal rigidity, bulging fontanelle, photophobia, and a positive Kernig's or Brudzinski's sign.[13] Seizures are present in 20% to 30% of children with bacterial meningitis.[15] Other signs like shock, disseminated intravascular coagulation (DIC), purpuric rash, and coma are more common in meningococcal meningitis.[14] In this study we also found that a specific triad comprising of fever, poor oral intake and seizures were the most common presentations.

Gram stain has helped clinicians to decide on the choice of empirical antimicrobials. Recently, Diederik, reported that bacterial pathogen can be detected on a CSF Gram stain.[15] In our study, we found that although the microorganism was not seen during microscopic examination; the culures were positive. Among the Gram positive bacteria, the coagulase negative staphylococcus, *S. aureus* and *Streptococcus* spp were common. If present, they are easily visible between the neutrophils.

Meningitis most commonly presents with a negative Gram stain and it is often considered an enteroviral meningitis with a benign clinical outcome. As such, used alone; the Gram stain could be an insensitive method to diagnose bacterial meningitis.

Therefore, in this study, the clinicians also replied on clinical presentations and several laboratory parameters such as gross appearance of the CSF, TWBC and the result of latex agglutination test. In this study, the organisms were isolated from CSF samples. In our hospital site, positive culture and sensitivity test was 11.1%.

Nonetheless a positive Gram stain result helps clinicians to choose suitable antimicrobial treatment for either Gram negative or Gram positive bacteria while waiting for the relevant culture result. The standard approach to the treatment of meningitis caused by *Staphylococcus aureus* occurs mainly after neurosurgical procedures or placement of CSF shunts. Antistaphylococcal penicillins are more effective than vancomycin for the treatment of severe *S aureus* disease, but empirical vancomycin can be used until susceptibility testing results are ready.[16-17]

From Malaysia, Hussain *et al.* (1998) noted that bacterial meningitis patients who were below the age of five years, had a mortality rate of 12.5% and 21 patients (30%) suffered neurologic sequelae. In our study, we found higher mortality rate (31.2%) than the previous study done by Hussain *et al.* (1998), which was probably due to the differences in the aetiological agent and underlying illness. In this study, twenty patients had suffered from neurological deficient: five had nerve palsy, five had paralysis, four had increase muscle tone, four had skin rash and three had diarrhea (table 3). Evidence indicates that mortality of meningitis among children aged less than 15 years old ranged from 19.6% to 34%.[18-19] Mortality is frequently seen among patients with pneumococcal meningitis.[19, 20]

There are several prognostic factors involved in the outcome of meningitis. Aetiological agent, primary brain disease, initial consciousness level, very low CSF glucose concentration, presence of bacteremia, and inappropriate antibiotic use have been reported as important risk factors of mortality.[21-24] Unlike other studies, we found that young age and altered consciousness were the only two significant factors associated with mortality.

This study was limited to one tertiary centre hospital. The patients in this study do not represent the population of meningitis cases within Malaysia. Further research is needed to obtain more understanding of hospital bacterial meningitis, especially in comparing between types of

hospitals, patients' risk factors, and outcomes among survivors.

CONCLUSION

Infectious meningitis is a big health concern, especially among children. The clinical presentation has not changed in hospital acquired bacterial meningitis compare with community acquired bacterial meningitis. The causative microorganisms in this study focused on hospital associated pathogens in keeping with our hospital setting and attention in neurosurgical management. Clinicians should be alert for changes in presenting symptoms and modify their choice of empirical antimicrobial therapy accordingly. Since high mortality is linked to hospital acquired meningitis, there is a need for physicians to focus attention on patients presenting significant prognostic factors, especially among younger aged patients.

Conflicts of interest: None declared

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