Bacteria Meningitis: Problems Of Empirical Treatment In A Teaching Hospital In The Tropics

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Citation

Abstract

Bacteria meningitis (BM) is commonly associated with high fatality. This study was conducted in Ladoke Akintola University Teaching Hospital, Osogbo, Nigeria, with the view to assessing the outcome and usefulness of empirical therapy of BM. Medical records of patients with BM managed in the year 2004 and 2005 were retrieved and demographic, clinical and laboratory data obtained analyzed using GraphPad computer software. Records of 172 patients were available for analysis; age range was 1day - 80 years, M: F ratio 1.7: 1. Mortality rate was 45.6%; 38.3% had favourable outcome, 8.1% had varying neurological sequelae and 11.5% discharged self against medical advice. Cerebrospinal fluid (CSF) analysis was done in only 68 patients; 30 had CSF parameters suggestive of BM; Gram stain was positive for bacteria in only 18 (26.5%) and culture in 6 (8.9%). Outcome was poorer in dehydrated patients (P=0.032), cases without CSF investigations (P=0.0001), and those who did not receive antibiotics (P=0008). The only empiric antibiotic combination with significant favourable outcome was penicillinG and chloramphenicol (P=0.021). This result shows that empirical treatment of BM is associated with high case fatality.

INTRODUCTION

Since the first recognition of bacteria meningitis (BM) in 1805[1], mortality from this infection has remained unacceptably high and developmental disabilities and neurologic sequelae following neonatal and infantile meningitis still occur in significant number of survivals. Specific aetiological diagnosis of BM in developing countries is often difficult. Although Gram staining of CSF sediment is a very useful cheap and fairly rapid method of identification of organism, the sensitivity in developing countries is only 25-40%[2] when compared to 80-85% in developed countries[3]. Cultures of CSF are also infrequently performed in many health institutions in developing countries and sensitivity does not exceed 40% with results available only after 2-3days[2,4]. Other methods such as latex antigen tests (LAT)[5] and polymerase chain reaction (PCR)[6] that are highly sensitive and specific are expensive and not available for routine use in developing countries.

In Nigeria, epidemics of meningitis due to Neisseria meningitidis have been reported from the Northern region since the 1950s[7,8,9,10,11,12], and in the South, epidemic and sporadic cases[13,14,15,16,17,18] of BM due to Streptococcus pneumoniae, Haemophilus influenzae and enteric Gram negative bacilli have been reported by different tertiary health institutions. Several reviews[19,20,21] have suggested that the choice of antimicrobial agent for the initial empiric therapy of bacterial meningitis when there is no CSF Gram stain result or when CSF Gram stain is not diagnostic, should depend on the age, geographical location and immunological status of the patient.

In many tertiary health institutions in Nigeria, financial constraints have compelled many clinicians to employ empiric therapy for patients with meningitis without CSF analysis or culture. In this study, we assess the use of empiric therapy for suspected BM in our institution in order to determine its suitability in a resource poor country.

MATERIALS AND METHOD

Medical records of 172 patients clinically diagnosed and managed as BM in Ladoke Akintola University Teaching Hospital, Osogbo, between 2004 and 2005 were retrieved for analysis. Information retrieved included demographic data, height, weight, presenting complaints, results of physical examination, predisposing factors, complications, outcome and problems encountered during management. In those investigated, results of microbiological and other laboratory investigations were also retrieved.

Data entry and management were done with Microsoft Excel

on IBM ThinkPad computer. All analyses and calculations were performed using GraphPad software (GraphPad Software Inc, San Diego, USA). Relationship between categorical variables was done using Chi square or Fisher's exact test and for continuous variables using Student's t-test or Mann Whitney test as appropriate and $P < 0.05$ was taken as significant value.

RESULT

DEMOGRAPHIC CHARACTERISTICS

Of the 172 patients with suspected BM reviewed over the study period, 108 were males and 64 were females giving a male to female ratio of 1.7 to 1. The age of the patients ranged from 1 month to 80 years. The age group 16-50 years constituted the majority (36.2%) followed by age group above 50 years (18.6%), 6-15 years (17.4%), 1-5 years (12.8%), infants (8.1%) and neonates (8.1%) (Table 1).

Figure 1

Table 1: Age and sex distribution of patients with meningitis in LAUTECH Teaching Hospital (2004-2005)

Age group/Sex	Male	Female	Total (%)
0-4weeks	12	2	14 (8.1)
5weeks-11months	6	8	14 (8.1)
1-5 year	16	6	22 (12.8)
6-15 year	12	18	30 (17.4)
16-50 year	42	14	56 (32.6)
> 50 year	16	16	32 (18.6)
Ungrouped	4	0	4 (2.3)
Total	108	64	172 (100)

DIAGNOSIS

The common symptoms at presentation were fever in 75.6% of cases, impaired consciousness (50.0%), headache (32.6%), convulsion (27.9%), neck stiffness/pain (18.6%) and others (45.9%). Signs of meningeal irritation such as neck stiffness, Kernig's, Brudzinski and Babinski were found in only 62.8%, 43.0%, 33.7% and 6.2% respectively (Table 2).

Figure 2

Table 2: Clinical manifestations of meningitis in LAUTECH Teaching Hospital

Clinical features	Number of patients	Percentage
Symptoms		
Fever	130	75.6
Impaired consciousness	86	50.0
Headache	56	32.6
Convulsion	48	27.9
Neck pain/stiffness	32	18.6
Others (Constitutional symptoms)	79	45.9
Signs		
Fever	132	76.7
Neck stiffness	108	62.8
Altered consciousness	102	59.3
Kernig's signs	74	43.0
Brudzinski sign	58	33.7
Babinski sign	10	6.2
Palor	59	34.3
Dehydration	36	20.9
Jaundice	16	9.3
Bulging anterior fontanelle	6	3.5
Plantar response	4	2.3
Cranial nerve palsy	10	5.8

Only 68 (42.0%) patients were investigated by CSF microscopy and culture. CSF cell morphology (protein > 45mg/dL, WBC > 50cells/ml and sugar < 2.2mmol/L) was suggestive of BM in 30 (41.1%) patients, 18 (26.5%) of these were positive for bacteria on Gram stain and 6 (8.8%) of these 18 had positive culture, Streptococcus pneumoniae in 5 and Escherichia coli in 1 (Table3).

Figure 3

Table 3: CSF parameters among patients with bacterial meningitis in LAUTECH Teaching Hospital (n = 68)

CSF parameters	Characteristics	Number of patients (%)
Appearance	Clear	32 (47.1)
	Turbid	30 (44.1)
	Xanthochromic	6 (8.8)
CSF sugar	2.2-4.4mmol/l	34 (50.0)
(Range = 0.7-5.4mmol/l)	< 2.2mmol/l	30 (44.1)
(Mean = 2.7mmol/l)	> 4.4mmol/l	4 (5.9)
CSF protein	15-45 mg/dl	20 (29.4)
(Range = 9-1454 mg/dl)	> 45mg/dl	44 (64.7)
Mean = 207mg/dl	< 15mg/dl	4 (5.9)
CSF WBC count	0- 50 WBC/ml	12 (17.6)
(Range = 50-1200 WBC/ml)	50-1000 WBC/ml	54 (79.4)
Mean = 636/ml	> 1000 WBC/ml	2 (2.9)
CSF Gram stain	G+ve cocci	17 (25.0)
	G-ve bacilli	1 (1.5)
CSF culture	Streptococcus pneumoniae	5 (7.4)
	Escherichia coli	1 (1.5)

OUTCOME

Sixty two (38.3%) patients recovered completely before being discharged home, while 10 (8.1%) had varied neurological deficits (such as cranial nerve deficit, exaggerated deep tendon reflexes, quadriparesis and quadrilplegia) and 20 (10.5%) discharged self against medical advice (Table 4).

Figure 4

Table 4: Outcome of treatment of meningitis in LAUTECH Teaching Hospital

Outcome/Sex	Male	Female	Total (%)
Survived	44	18	62 (36.0)
Survived with neurological deficit	4	6	10 (5.8)
Died	52	28	80 (46.5)
Discharge against medical advice	8	12	20 (11.6)
Total	108	64	172 (100)

A total of 80 patients died giving a mortality rate of 45.5%. Mortality was significantly associated with severe dehydration (P=0.0319), those who did not have CSF microscopy or culture performed (P<0.0001) and those who did not receive antibiotic therapy (P=0.0008). (Table 4). The antibiotic combination that was significantly associated with favourable outcome was penicillin and chloramphenicol (P=0.021). Ampicillin/gentamicin (P=0.54), ampicillin/chloramphenicol/cephalosporins (P=0.41) and ampicillin/gentamicin/cephalosporin (P=0.46) combinations did not significantly influenced outcome. The presence of clinical symptoms such as convulsion, impaired consciousness and jaundice also did not significantly influenced outcome (P > 0.05). The greatest problem encountered during the course of patients care in this series was financial constraint as many patients were unable to pay for investigations and medications.

Figure 5

Table 5: Prognostic factors of meningitis in LAUTECH Teaching Hospital

Factors	No of patients used for analysis	No with favourable outcome	No with poor outcome Death	Neurologic deficit	P value
Age group 16-50 years*	56	14	42	0	0.003
Convulsion	44	22	22	0	0.15
Altered consciousness	102	42	52	8	1.0
Dehydration*	28	6	20	2	0.03
Jaundice	10	4	4	2	1.0
Neck stiffness	104	46	50	8	0.21
Kernig's sign*	60	32	24	4	0.01
Brudzinski sign*	58	30	24	4	0.04
Babinski sign	10	4	6	0	1.0
CSF analysis performed**	68	44	18	6	0.0001
CSF analysis not performed**	84	20	54	10	0.0001
Crystalline penicillin/Ccol*	66	34	24	8	0.02
Ampicillin/Gentamicin	12	6	4	2	0.54
Amp/Ccol/Cephalosporin	30	10	18	2	0.41
Amp/Gent/Cephalosporin	20	10	8	2	0.46
No antibiotic**	14	0	14	0	0.001

All 20 patients discharged against medical advice were excluded from analysis
*Statistically significant
**Extremely statistically significant

DISCUSSION

The result of this study showed that mortality from BM in Osogbo, Southwestern Nigeria is unacceptably high. The 45.6% mortality rate in this series is far higher than reports of previous studies in other parts of the country[13,14,15,16,17,18] and elsewhere.[22] This underscores the fact that BM still remains a fatal disease with high mortality, and morbidity in those who recovers.[22,23] The outcome of this infectious neurological disease has been shown to largely depend on age, type of organisms, time of initiation and appropriateness of antibiotic therapy, other intercurrent illnesses and immunological status of patient affected.[19,20,21] The high mortality in this report might not be unconnected with the fact that more than half (60%) of the patients were treated empirically without any recourse to CSF investigation. The likelihood of using inappropriate antimicrobial agents is high with empirical therapy.

Mortality from BM in our study was significantly higher in cases with dehydration and in cases where basic CSF investigations and antibiotic therapy could not be administered due to financial constraints. Especially in those who did not receive antibiotics, mortality was 100% indicating the grave consequence of BM in those who are not financially empowered in the society and also lend credence to the fact that BM is invariably fatal. Mortality was also high (60%) in cases of BM due to S. pneumoniae in this study and agrees with similar studies[13,18]in Southern Nigeria. Although BM due to Gram negative enteric bacilli, which is usually associated with high mortality, tends to be more prevalent in neonates[23], an inference cannot be made about this assertion in our study because of the small number of neonates involved.

Apart from the combination of crystalline penicillin and chloramphenicol therapy, which gave a statistically significant favorable outcome, other combination regimen such as ampicillin/gentamicin, ampicillin/chloramphenicol/cephalosporin and ampicillin/gentamicin/cephalosporin gave comparable but poorer outcome. Our observation of a favorable outcome with penicillin/chloramphenicol combination corroborates the findings of Ozumba[18] who used the same combination in Enugu, a centre in the same meningitis belt as our centre. However, some recent studies have shown an increase in the incidence and dissemination of strains of S. pneumoniae resistant to penicillin and cephalosporins[24], and strains of H. influenzae resistant to ampicillin and chloramphenicol[25], and the possibility of some of these resistant organisms being involved in BM in our series is very high. This may partly explain the high mortality recorded.

Aside from fever which was present in about 75% of patients, symptoms such as convulsion, altered consciousness, headache and neck pain/stiffness were found in less than 50% of our patients, and these symptoms were notably absent in the neonates. The classical signs of meningitis such as Kernig's and Brudzinski signs were

elicited in less than 40% of patients, although when present were associated with poor prognosis. The implication is that clinical diagnosis alone is inadequate as a diagnostic modality for BM, especially in our environment where antibiotic abuse/misuse tends to modify the classical symptoms of BM and therefore creates diagnostic difficulties to unsuspecting physicians. Also, the presence of convulsion and impaired consciousness, which were associated with high mortality in some series[25], did not significantly influenced outcome in this study. Their presence should therefore not be seen as a discouraging sign but rather as a challenge to proper investigation and management.

The CSF parameters (sugar, protein and white cell counts) were suggestive of BM in 41% of those investigated by CSF analysis while the 26.5% sensitivity of CSF Gram stain in the study is comparable to what is normally obtained in developing countries[4] but culture is correspondingly less sensitive. Factors that may be responsible for this include frequent inappropriate use of antibiotics before presentation, delay in processing of CSF specimens and lack of laboratory facilities to isolate fastidious organisms. For mortality from BM to appreciably decrease, these factors must be addressed.

CONCLUSION

Our study shows that empiric antibiotic therapy of BM without CSF investigations is associated with extremely high case fatality. We suggest that in a resource poor country like Nigeria with widespread abject poverty, the initial management of BM especially the cost of performance of basic CSF investigation and antibiotic therapy should be borne by the government through the hospital management while the choice of empiric therapy should be guided by research findings.

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