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Causes and outcome of bacterial meningitis in Malawian children

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ABSTRACT

598 children with bacterial meningitis were admitted to the paediatric wards of the Queen Elizabeth Central Hospital (QECH), Blantyre, Malawi from July 1997 – March 2001. Patients were followed up at 1 and 6 months after hospital discharge when physical, neurological, developmental and hearing assessments were made. The most common causes of pyogenic meningitis were *Streptococcus pneumoniae* (40%), *Haemophilus influenzae* type b (28%), *Neisseria meningitidis* (11%), *Salmonella species* (5%). There was no growth on culture in 13% of cases. The overall mortality was 31% and 38% were left with significant sequelae. Indicators for a poor prognosis were younger age, lower coma score on admission, bacterial cause, nutritional status and HIV positivity.

Introduction

Acute bacterial meningitis causes many deaths and significant long-term morbidity throughout the world. In resource poor countries the incidence of bacterial meningitis in children is about 10 times greater than that in well resourced countries. Case fatality is reported to be 12–50 % in poor countries, compared with 4.5% in developed countries.[2-6] Sequelae are reported in 15-20% of children in developed countries; in developing countries sequelae are probably underreported.[5-9] We recently studied the role of dexamethasone as an adjuvant therapy in bacterial meningitis. The results are reported elsewhere but showed no advantage in the use of steroids.[10] Here we report the overall findings of the children in the study as to cause, presentation, progress and outcome of the disease.

Methods

Children aged from 2 months to 13 years who were admitted to the QECH from July 1997 – March 2001, with bacterial meningitis were included. Meningitis was defined as the presence of ≥100 white cells, predominantly granulocytes, in an admission sample of cerebrospinal fluid (CSF), or a positive Gram stain showing bacteria in CSF, or the culture of bacteria from CSF.

Management protocol. All the children had a complete history taken and were fully examined and weighed. A lumbar puncture (LP) was done and if meningitis was suspected by the naked eye appearance of the CSF sample, an intravenous line was established. Blood samples were taken at this time for full blood count, malaria parasites (thick film), plasma glucose and electrolytes and blood culture. After parental counselling and with their agreement HIV status was assessed.

Benzylpenicillin 200,000 iu/kg/24 hours and chloramphenicol 100mg/kg/24hours were given 6 hourly. As soon as the sensitivities of the causative bacteria were known the appropriate antibiotic was continued and the other was stopped. If there was no growth on culture both antibiotics were continued. Antibiotics were continued for 10 days in all cases except meningococcal meningitis when the course was 7 days, or salmonella meningitis, when antibiotics were continued for 3 weeks. Antibiotics were given intravenously for at least 72 hours and were continued parenterally until the child was well enough to take medications orally, in which case, if the child was on chloramphenicol, this was given by mouth.

Ceftriaxone 50mg/kg/12 hourly IV or IM for 7 days was given as the second line antibiotic. It was given if repeat lumbar puncture showed the continued presence of bacteria or if the clinical picture was not improving, or had deteriorated. During the study it was noted that *Haemophilus influenzae* were increasingly resistant to chloramphenicol *in vitro* (Table 1).

Table 1. Causative bacteria and antibiotic susceptibility

Causative agent	Total	Resistance to antibiotics Chloramphenicol (%)	Penicillin (%)
Streptococus pneumoniae	229	39 (17)	47 (20)
H. influenzae type b	170	33 (19)	170 (100)
Salmonellae spp	29	7 (24)	29 (100)
N. meningitidis	63	0	0

After this, if the Gram stain of the CSF was available on admission and showed Gram-negative rods, ceftriaxone was given as initial treatment instead of chloramphenicol. This occurred on 39 occasions.

Supportive Care

Intravenous fluid was given in maintenance volumes, calculated according to body weight, as ½ strength Darrow's in 5% glucose solution. If shock was present this was corrected with boluses of 20ml/kg of normal saline solution titrated against capillary refill and clinical improvement in the standard manner. If the baby was breast feeding and able to suck, intravenous fluids were

infused as slowly as possible. If a child remained in coma and was unable to feed for longer than 48 hours, a nasogastric tube was inserted and 2 hourly feeds were given.

Hypoglycaemia (blood glucose ≤2 mmol/L) was corrected with 1ml/kg of 50% glucose given slowly into a fast-running IV line. Anaemia was corrected with a blood transfusion when the haematocrit was below 15% or when the clinical condition warranted it.

All children with malarial parasitaemia were treated with parenteral quinine until able to swallow, and then oral suphadoxine-pyrimethamine was prescribed. Seizures were treated with paraldehyde 0.1ml/kg IM after hypoglycaemia was excluded or

corrected. If seizures were uncontrolled after 2 doses of paraldehyde, a loading dose of 15mg/kg of phenobarbitone IM was given followed by 12 hourly maintenance doses of 5-8mg/kg/body weight.

Assessment on discharge and at follow-up visits

Every child was assessed before discharge from hospital, and at one month and six months after discharge for neurological, developmental, visual and hearing difficulties. Head circumference was recorded on admission, at the time of discharge from hospital and at each subsequent visit. An ultrasound scan of the brain was obtained in children with an open fontanelle. This procedure was used for management of possible complications and was carried out routinely on discharge from hospital or sooner if the patient's condition warranted it.

Behavioural tests were carried out by 2 trained nurses at each follow up visit, and more frequently if equivocal results were found on testing. Babies were followed up until they were old enough for behavioural testing or until seen by an audiologist. Each child had the ears examined and standard behavioural hearing tests conducted. Tympanometry was done and oto-evoked emissions testing was used, when appropriate.

Data

Data were entered in a Microsoft Excel file. This was double checked and analysed with Epi Info.6.

Results

Four bacteria caused the majority of cases of bacterial meningitis, S.pneumoniae, H. influenzae type b, N.meningitidis and Salmonellae spp.

Findings at presentation, overall and by causative agents.

Table 2 (below) shows the clinical findings at presentation overall and by each causative agent. Over a third of children had received antibiotics prior to admission. Cotrimoxazole (24%) penicillin (52%) usually orally, and others (4%). Six children were on tuberculosis (TB) treatment. Only 2 children with sickle cell disease were identified in the study. Both were HIV negative and both had *S. pneumoniae* infections.

Progress during illness

Table 3 shows the progress of patients during the hospital stay. The doses of anticonvulsant drugs given ranged from 1 to 45, 72% (n = 80) received ≤2 doses and 9% (n = 10) received > 10 doses. Second line antibiotic therapy, usually with ceftriaxone, was more commonly required for H. influenzae and salmonella meningitis than for pneumococcal and was not required for meningococcal meningitis. 39 children were started directly on to ceftriaxone because Gram negative rods were identified on Gram stain of CSF.

Nine subdural collections were tapped. No CT scans were carried out and so complications such as these could only be detected and dealt with in children in whom the fontanelle was patent. Ultrasound scans of the head were done in 151 of 299 children with a patent fontanelle. Some children died before a scan could be arranged or missed being scanned before discharge. Among children who underwent ultrasonography (USS) through a

Table 2. Clinical findings on presentation of bacterial meningitis by causative agent

Causative Agent (%)	*Overall* n = 598*	*S. Pneumoniae* n =238 (40)	*H. Influenzae* n = 170 (28)	*N.Meningitidi* N = 67 (11)	*Salmonella sps* n= 29 (5)	*No growth on culture* n = 78 (13)	*Other≠* n = 16 (3)
Number of children	598	238	170	67	29	78	
Median Age(months)	13.5	27	8	90	15	40	
Range	[2-168]	[2 –168]	[2-96]	[3-168]	[2 - 48]	[2 – 156]	
Male: Female	338:260	123:105	100:70	40:27	20:9	50:28	
Mean Wgt for Age %	79.1	77.2	82.7	78.7	78.	79.1	
Range	[39 - 126]	[39-126]	[39-126]	[41-133]	[49-113]	[44-126]	
Median fever (days)	3	2 .5	3	2	11	2.5	
Range	[0 – 60]	[0 – 25]	[0 – 60]	[0 – 21]	[0 – 21]	[0 – 30]	
≤2 days fever	268 (45)	117 (49)	62 (36)	37 (55)	9 (31)	33	
History of seizures	286 (49)	129 (54)	79 (46)	15 (22)	12 (41)	34	
Focal Fits(%of fits)	61 (21)	33 (25.5)	12 (7)	4 (6)	3 (8)	5	
Not sucking	275 (46)	135 (48)	66 (39)	26 (39)	11 (38)	28	
Prior antibiotics	214 (36)	80 (34)	74 (43.5)	10 (15)	14 (48)	26	
Ear infection	71 (12)	35 (15)	15 (9)	3 (4)	2 (7)	10	
Focus of infection	108 (18)	48 (20)	27 (16)	4 (6)	7 (24)	13	
Coma Score ≤2	209 (35)	100 (42)	58 (34)	10 (15)	11 (38)	23	
Skin rash	32 (5)	18 (7.5)	4 (2)	1 (1.5)	1 (3)	6	
Generalised LN++	50 (8)	27 (11)	4 (2)	4 (6)	6 21)	6	
Shock	53 (9)	21 (9)	13 (8)	6 (6)	3 (8)	9	
Mean Bd glucose	5.9	5.9	5.9	5.8 (9)	5 (7)	5.7	
Range: mmol/L	[0 – 37.3]	[0 – 14.5]	[0 – 37.3]	[0 –11.6]	[1 – 8.1]	[1.5 – 9.6]	
Mean Temp 0C	38.1	38.5	37.8	37.9	37	37.8	
Range	[34.5 - 40.8]	[35 – 40.6]	[34.5-40]	[35.4 - 40]	[35 – 40]	[35 – 40.8]	
Mean Haemaglobin	8.6	8.6	7.6	10.9	6.9	9.3	
Range mg/dl	[2 – 14.8]	[2 – 13.9]	[3 – 12.8]	[5.5 –14.8]	[4.8-10.9]	[4.9-13.2]	
Na (meq/l)	132	132	132.4	132.4	131	133	
Range	[115-153]	[119 –153]	[115-153]	[124-141]	[118 –144]	[98.5 –153]	
Malaria parasites +	51 (8.5)	35 (15)	26 (15)	16 (24)	4 (14)	12	
HIV negative	143 (24)	99 (41.5)	98 (58)	33 (49)	14 (48)	51	
HIV positive	157 (26)	103 (43)	32 (19)	4 (6)	10 (34)	15	
HIV not tested	138 (23)	46 (19)	39 (23)	30 (45)	5 (17)	15	

* includes 16 cases caused by Group B *streptococcus* 2, other *streptococci* 5, *staphylococci* 1, *E.Coli* 3, other Gram negative rod bacteria 5.
Meningococcal infections were 51 group A, 6 group B, 9 non A,B,C. *Salmonellae sp* were 21 *S.typhimurium* and 8 *S.enteritides*.

Table 3: Progress and early outcome

	N (%)
Total	598
Number requiring anticonvulsant therapy	245 (41)
USS of head done / number with patent fontanelle	152
Abnormal findings USS	61
Number requiring 2nd line antibiotic therapy	189 (32)
Subdural/abscess tapped[1]	13
Blood transfusions[2]	18
Absconded	6 (1)
Alive and fully recovered[3]	159 (26.5)
Died in hospital	181 (30)
Sequelae on discharge	105 (17.5)
?sequelae on discharge	47 (8)

[1] Includes 2 brain abscesses (*Salmonellae sps* 1 ventricular tap (*S.pneumoniae*) and 1 necrotic post infarct abscess (E.Coli)
[2] Transfusions given on admission or during stay in hospital; includes 1 *E.Coli* in steroid group
[3] 10 died of unrelated illness in the next 12 months, 18 had inconclusive hearing tests and 5 were not tested on follow up.

patent fontanelle, abnormal findings were most common in salmonella (9/11 = 81%) and H. influenzae (29/68 = 42%) meningitis, and were less common in pneumococcal (11/41=27%). Numbers (4/7=59%) were few in the meningococcal infections.

Outcome on discharge from hospital, overall and by causative agent.

Table 3 (above) shows the outcome on discharge from hospital and table 4 the outcome for those who were discharged alive. Meningitis caused by *Salmonella spp* had the highest in-hospital mortality (15/29, 58%). Meningococcal meningitis had a much better outcome than the other groups with a mortality of 3/66 (4.5%). 348 (83%) children discharged from hospital were seen at follow up. Thirty six children were not seen at follow up, 30 of whom had made a full recovery and were old enough to have had full neurological and hearing assessments done while in hospital. Six children who had sequelae on discharge were not found. Thirty-four children had died within 6 months of discharge, 19 from meningitis related problems (18 of these were sent home with severe sequelae), and 15 of unrelated illnesses, such as malaria. Many children had more than one type of sequelae.

Final outcome by causative agent

In *S. pneumoniae* meningitis the mortality was 41%. Neurological sequelae were found in 31% (48/156) of survivors and 53 (33%) had hearing loss attributed directly to the meningitis. In *H. influenzae* type b meningitis, overall mortality was 25% (42/170). On follow up 47% of children had made a complete recovery. Hearing sequelae occurred in 15.4% (19/123). Neurological sequelae were found in 41 (33%) of survivors. Meningococcal meningitis had a better overall outcome than infections due to other bacteria. Mortality was 4.5% and 23% were left with sequelae. Children with meningococcal infections were older (median age 91.5 months) than those admitted with other infections (median age 13.5 months), and fewer were HIV positive. 15 of 63 were left with hearing sequelae. Six children who had been discharged with isolated cranial nerve palsies had all made a complete recovery when reviewed one month after discharge. In children with salmonella meningitis the mortality was 58%. Ten of fifteen (67%) survivors were neurologically damaged and 6 (40%) were left with hearing impairment.

Outcome by other factors

Ceftriaxone was used as first line therapy in 31 patients with *H. influenzae* meningitis. Mortality was marginally lower in these patients than in those who were treated with penicillin and chloramphenicol alone (10% v 22%, p= 0.12). Sequelae were the same (29%v29.7%) in each group.

Overall, HIV-positive children had a higher case-fatality rate than HIV negative children. HIV-positive children were more malnourished (median WFA 73%v 81%), than HIV-negative (p<0.00001). Though 17% of all the patients tested were confirmed as HIV positive, 47% of deaths in tested cases were in seropositive children. The number of sequelae was uninfluenced by HIV serostatus except in *S.pneumoniae* meningitis when HIV positive children were left with more sequelae (p=0.032). Recurrent meningitis occurred in 19/157 (12%) HIV positive children compared to12/303 (3%) in seronegative patients (p=0.00018). A third (16/50) of recurrent infections were due to S.pneumoniae.

Table 4. Outcome of survivors from hospital by causative agent

Causative Agent Number discharged alive	Overall* n = 432	S.Pneumoniae n = 156	H. Influenzae N = 123	N.Meningitides n =66	Salmonella spp n =15	No growth n = 57
Died after discharge of meningitis related problem	19 (4)	11 (7)	5 (4)	1 (1.5)	2 (13)	0
Died after discharge of non meningitis problem	15 (3)	7 (4)	1 (0.8)	2 (3)	1 (6)	3 (5)
Total seen at follow up	348 (80.5)	128 (82)	107 (87)	57 (86)	10 (67)	53 (93)
Full recovery[1]	233 (54)	69 (44)	70 (57)	48 (73)	2 (13)	38 (67)
Total with sequelae[1]	165 (29)	71 (45.5)	47 (38)	15 (23)	10 (67)	16 (28)
All with neurological problems	125 (29)	46 (29)	41 (33)	8 (12)	11 (73)	15 (26)
All with hearing loss	127 (29)	60 (38)	29 (23)	15 (23)	6 (40)	13 (23)

*. includes 15 caused by a variety of bacteria
[1]. 38 non attenders are included in the outcomes.
30 were fully recovered on discharge and old enough to be assessed for neurological and hearing ability
6 had sequelae on discharge of whom 6 had neurological damaged, (2 S. pneumoniae, 3 H. influenzae, 1 salmonella sps) and 3 also had hearing impairment (H. Influenzae)

Prior antibiotic use did not affect clinical features at presentation or response to treatment. No relationship was found between the duration of symptoms and the course or outcome of the disease. Differences between survivors, children who died and those left with sequelae

A logistic regression analysis showed that poor outcome was associated with age (> in the younger age group, p=0.053), malnutrition (p=0.046), a low coma score (Blantyre Coma Score ≤2)*, on presentation (p=0.00001), HIV seropositivity (p=0.029), and the causative agent (p=0.001).

Discussion

The incidence of meningitis in resource constrained countries is 100 – 160/100,000 population, the mortality is 12 –50% and sequelae are probably underreported. [5-9] In developed countries the incidence is ≈16/100,000 children under 16 years of age with a CFR of ≈ 4.5% and sequelae in ≈15–20% of survivors.[1-3,10,11]

In our study patients presented late, (median days of fever = 3 days), 48% had a history of convulsions and 35% had a Blantyre coma score of ≤ 2. The case fatality rate was 31%, and 38% of survivors were left with sequelae. The mortality rate of 31% was a reduction from a previously recorded 50%[12] but this improved survival is due to increased monitoring and careful management of all the children.

The mortality was greatest in salmonella meningitis (58%) and least in meningococcal infections (4.5%). Altered consciousness, the presence of HIV positivity and malnutrition were independent significant predictors of a poor prognosis. Prior antibiotic treatment and length of illness did not affect outcome.

During this study the first line antibiotic treatment was chloramphenicol *and/or* penicillin. Table 1 shows the susceptibilty patterns of the common bacteria that cause meningitis to these drugs. In a small subgroup of patients in whom ceftriaxone was used as a first line therapy overall mortality was reduced.

In most developing countries the first line antibiotics are cheap and available but are given against a rising, and often unquantified, resistance to these antibiotics of the bacteria that commonly cause meningitis. Poor nutrition, anaemia and immunosuppression from chronic disease such as HIV often underlie the acute bacterial infection. Delays in presentation are common. Immunisation, which has proved to be so successful in developed countries in preventing invasive *Haemophilus influenzae* type b infections is now included in the Extended Programme of Immunisation (EPI) in Malawi. We can look forward to a reduction in the number of children presenting with Hib infections but increasing resistance of bacteria to chloramphenicol and penicillin is a matter of great concern.

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