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Childhood bacterial meningitis in Mbarara Hospital, Uganda: antimicrobial susceptibility and outcome of treatment.

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ABSTRACT

Background
The recommended antibiotic treatment of bacterial meningitis has come under scrutiny following frequent reports of *in-vitro* resistance by the common causative organisms to penicillin and chloramphenicol.
Objective
The study recorded the causative organisms, antibiotic sensitivity patterns and outcome of treatment of bacterial meningitis in children and examined the impact of various factors on the recorded outcome.
Design
This was a retrospective review of all case records of patients treated for bacterial meningitis over a one-year period.
Setting
The study was set in the paediatric wards of Mbarara University Teaching Hospital, in south western Uganda.
Results
A total of 77 patients were treated. Among 56 patients with available CSF results the frequency of bacterial causes was as follows: *H. influenzae* 13(23.2%), coliforms 7(12.5%), uncultured Gram-negative bacilli 7(12.5%), *S. pneumoniae* 5(8.9%) and *N. meningitidis* 3(5.4%). Most isolates tested were resistant to both penicillin and chloramphenicol, but all were sensitive to ciprofloxacin and perfloxacin. Twenty eight(36.8%) patients died,22(28.9%) survived with sequelae and 15(19.7%) improved without sequelae. 14/18 who received perfloxacin and/or ciprofloxacin survived compared with 23/47 who did not: p=0.04).
Conclusions
The high case-fatality rates and the high frequency of resistance to penicillin and chloramphenicol makea case for a review of the currently recommended antibiotic treatment of bacterial meningitis in this region. Fluoroquinolones need further evaluation as potential alternatives to chloramphenicol in the treatment of bacterial meningitis.
Keywords:
childhood bacterial meningitis, antimicrobial susceptibility, and treatment outcome.
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INTRODUCTION

Bacterial meningitis has for a long time been treated with a combination of penicillin/ampicillin and chloramphenicol, and this combination is still the widely recommended first choice in most of Africa. However the increasing frequency of reports of bacterial resistance *in-vitro* to these drugs has raised concern that this choice may no longer be appropriate.[1-3] There is a paucity of correlating data on clinical response to treatment, particularly from Africa, to back recommendations for a change in the current guidelines. There are, however, reports suggesting that chloramphenicol may be unsatisfactory in the treatment of meningitis caused by penicillin-resistant organisms.[4,5] On the other hand, a recent report from West Africa suggests that response to chloramphenicol-based regimens remains satisfactory.[6] Other reports, including a recent one from Uganda, suggest a much poorer response.[7]

We therefore set out to investigate the outcome of treatment of bacterial meningitis in our paediatric patients, and to examine various factors affecting this outcome.

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METHODS

We retrospectively reviewed the case notes of all patients treated for bacterial meningitis in the paediatric wards of Mbarara University Teaching Hospital (MUTH) over a one-year period from 1 January to 31 December 1999.

Information recorded included; age, presenting symptoms and signs, bacteriological diagnosis, antimicrobial sensitivity where available, duration of symptoms before presentation to hospital, and duration of hospital stay before initiation of antibiotic therapy.

The outcome of treatment was recorded as; improved without sequelae (1), improved with sequelae (2), died (3), or absconded (4). For the purpose of analysis of factors influencing outcome the patients were regrouped into two groups, excluding absconders thus, survivors (outcomes 1 and 2) and deaths (outcome 3).

Data were analysed using the Epi Info version 6.04 statistical analysis package. To examine the impact of various risk factors on the outcome risk ratios were used for the comparison of proportions between the two major outcome groups. The student's t test was used to compare the mean duration of symptoms between survivors and deaths. The level of significance was set at $p=0.05$.

RESULTS

A total of 77 patients were treated for bacterial meningitis during the study period. Results of cerebrospinal

fluid (CSF) analysis were available for 56 out of 66 patients on whom a lumbar puncture was performed. These are summarised in Table 1.

Table 1. Results of CSF analysis

Result	Number	% (n = 56)
Haemophilus	13	23.2
Coliforms	7	12.5
Gram-negative bacilli	7	12.5
Pneumococcus	5	8.9
Staphylococcus	5	8.9
Meningococcus	3	5.4
Streptococcus	1	1.8
Proteus	1	1.8
Others Turbid*	10	17.8
Traumatic	2	3.5
Xanthochromic	1	1.8
Cryptococcus	1	1.8

**Turbid CSF from a non-traumatic lumbar puncture was considered indicative of meningitis*

Fifty-three patients had confirmed meningitis (including 10 with turbid CSF but no bacteria identified). The remainder included two patients with traumatic lumbar punctures, one patient with xanthochromic CSF and 11 patients with no record of lumbar puncture at all.

The commonest aetiological agent was *H. influenzae* and this affected only the youngest children (age range 2 months to 2 years). The frequency of "unusual" aetiological agents was notably high in this group with coliforms and Gram-negative bacilli (uncultured) together accounting for as many cases as *H. influenzae.*

Results of *in-vitro* antibiotic sensitivity tests were available for only 19 out of 56 patients with CSF results.

Table 2. Antibiotic sensitivity patterns for selected aetiological agents

	Sensitivity to antibiotics							
Aetiological agent (no. tested)	PEN	AMP	AUG	PELOX CIPRO	GENT	ERYTH	CHROR	CLOG
H. influenzae(8)	0	5	4	8	2	3	3	0
S. Pneumoniae(2)	1	1	1	2	1	2	1	2
Coliforms (6)	0	0	3	6	4	1	1	0
S. aureus (1)	0	0	0	1	1	1	1	0

PEN = benzyl penicillin
AMP = ampicillin
AUG = amoxycillin + clavulanate (Augmentin)
PELOX = perfloxacin
CIPRO = ciprofloxacin
GENT = Gentamicin
ERYTH = Erythromycin
CHLOR = Chloramphenicol
CLOXA=Cloxacillin

The small number and the fact that no uniform antibiogram was used for all specimens made analysis of results of antibiotic sensitivity impossible. However it is worth noting that ciprofloxacin and perfloxacin were the only antibiotics that demonstrated *in-vitro* activity against all cultured organisms. Antibiotic discs for cephalosporins were not available during the study period.

Treatment and outcome

All patients were treated with chloramphenicol combined with crystalline penicillin or ampicillin as the initial antibiotic regimen. Eighteen patients (24%) were subsequently treated with ciprofloxacin/perfloxacin after cultures grew multi-drug resistant organisms. Fourteen of these survived. Ten patients were treated with cefotaxime even though susceptibilty testing for it was unavailable.

Thirty patients received a short course of dexamethasone as part of their treatment.

Results of treatment outcome are summarized in Table 3. Fifteen (19.7%) patients improved without sequelae while 22(28.9%) were discharged with neurological sequelae, mostly spasticity and hydrocephalus. A total of 28(36.8%) patients died whilst on treatment.

Table 3. Outcome of treatment

Outcome	Number	%
Improved without sequelae	15	19.7
Improved with sequelae	22	28.9
Died	28	36.8
Absconded	11	14.5
Total	**76**	**100**

Table 4 shows a summary of the results of a comparison of some risk factors for an adverse outcome between the two broad outcome groups, that is survivors and deaths. No single clinical feature independently predicted an adverse outcome.

A favorable outcome (survival) was more likely in those who received ciprofloxacin/perfloxacin (14/18 received vs. 23/47 not received, $p = 0.04$). No similar effect was demonstrable for dexamethasone treatment.

Table 4. Risk factors for adverse outcome

Factor	RR (95% CI)	P
Convulsions	1.5 (0.68-3.29)	0.2
Coma	1.79 (0.8-2.4)	0.373
Stiff neck	0.99 (0.55-1.76)	0.5
Pelox treatment	0.44 (0.18-1.0)	0.04*
Dexamethasone	1.01 (0.58-1.77)	0.5

** Patients who received perfloxacin and/or ciprofloxacin were more likely to survive.*

Delay in diagnosis and initiation of antibiotic therapy did not appear to have been an important factor in the high overall mortality. In the majority, the clinical diagnosis of meningitis was established and treatment instituted on the first day of hospitalisation. There was no significant difference between the two outcome groups either in the duration of symptoms before presentation, or in the length of hospital stay before initiation of antibiotic therapy. See Table 5.

Table 5. Duration of symptoms and length of hospital stay

	Outcome group			Difference between survivors and deaths
Mean duration (days)	Whole group	Survivors	Deaths	
D1	6.53	6.64	6.39	0.025 (p=0.87)
D2	0.4	0.3	0.5	1.246 (p=0.26)
D3	10.3	14	5.57	

D1 = duration of symptoms before presentation
D2 = duration of hospital stay before diagnosis/ treatment
D3 = time from initiation of treatment to outcome

Six patients (21.4%) died within 24 hours of admission, and 16 (57.1%) within 3 days, that is before results of culture and sensitivity could be available.

The mean age of patients who died was 16.5 months and that for survivors was 24.8 months. This difference was not statistically significant.

DISCUSSION

The antimicrobial therapy of bacterial meningitis has come under increasing scrutiny owing to numerous reports of antimicrobial resistance by the common causative organisms. This study demonstrates a significantly poorer response to a predominantly chloramphenicol-based regimen than what has been reported in various African centres.[1,8] A study in Nigeria done between 1993-1998 had a mortality of only 9/189 (4.8%), compared to ours of 36.8%, and concluded that response to chloramphenicol-based regimens remains satisfactory.[6] It also highlights various important differences between the patient groups studied that might account for this.

The commonest aetiological agent in this group was *H. influenzae* and this, together with coliforms and other gram-negative bacilli, accounted for 27 out of 77 (47%) of the cases. This pattern was similar to that recently found in a similar study in Kampala where *H. influenzae* together with Salmonella species accounted for 60% of the cases, and the case-fatality rate was similarly high (41.3%).[7] On the other hand, it is in contrast to the pattern recently reported from a bi-centre study in Nigeria[6] where the commonest organism was *N. meningitidis*, and the case-fatality rate only four per cent.

The size of the study was too small to allow proper comparison of antibiotic susceptibility patterns between different aetiological agents but it was apparent that isolates of *H. influenzae* and coliforms were frequently resistant to penicillin as well as chlorampenicol. Again this pattern would appear to be similar to that found in Kampala.[7]

There is limited experience with the use of fluoroquinolones in childhood meningitis as these are still not generally recommended for use in children. In this study ciprofloxacin and perfloxacin were the only antibiotics that were consistently active against all the bacterial species tested in-vitro. When available they were generally used as a last resort in those patients who failed to show clinical improvement on chloramphenicol, and whose micro-organisms showed multi-drug resistance *in-vitro*. It was gratifying to note that their use was largely satisfactory and they probably deserve further evaluation as potential second-line drugs.

Delayed presentation and treatment may have contributed to the high mortality in this patient group, although there was no obvious difference in duration of symptoms between survivors and deaths. However, the fact that almost 60% of the deaths occurred within the first 3 days of treatment (that is before culture results were available) emphasises the importance of an appropriate initial (empirical) choice of antibiotics. In many centres in Africa culture and sensitivity results are unavailable altogether and the choice of treatment will have to be dictated by locally appropriate guidelines.

In conclusion, the outcome of treatment of children with bacterial meningitis with the standard antibiotic regimen was largely unsatisfactory, with high case fatality rates. The relative frequency of *H. influenzae* and other gram-negative organisms, together with recently reported antimicrobial resistance to penicillin/ chlorampenicol are possible contributory factors. The high mortality rate makes a case for a review of the existing recommendations for initial therapy in this region. Fluoroquinolones need further evaluation as potentially cheaper alternatives to third generation cephalosporins as second-line drugs in the treatment of bacterial meningitis in Africa.

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