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Bacterial pathogens and outcome determinants of childhood pyogenic meningitis in Ilorin, Nigeria

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Summary

Empirical antimicrobial therapy remains justifiable in childhood pyogenic meningitis (CPM), but the continuing efficacy in a particular setting requires periodic microbiological surveillance. It was this need that informed the present five-year retrospective study of consecutive admissions for CPM at the Emergency Paediatric Unit (EPU) of the University of Ilorin Teaching Hospital, Ilorin, Nigeria. Of the 71 cerebro-spinal fluid [CSF] analyses, 41(57.6%) were Gram-smear positive (GSP). Gram-positive cocci (GPC) were identified in 23 (56.1%) smears, while 14 (34.2.%) had Gram-negative bacilli (GNB). Only three (7.3%) had Gram-negative diplococci (GND). Despite corroborative biochemical findings, the remaining 30 (42.3%), including two with tuberculous meningitis proved smear-negative. GPC cases had a mean age of 4.49 ± 5.3yrs, GNB, 3.06 ± 4.8yrs and GND, 4.47 ± 4.9yrs. CSF isolates were made in 28(39.4%) cases. *Streptococcus pneumoniae* accounted for a predominant 22 (78.6%) ($P = 0.00$), *Haemophilus influenzae* for 2 (7.1%), and *Neisseria meningitidis* for only 1(3.5%) case. Whereas *Strept. pneumoniae* and *H. influenzae* isolates were uniformly sensitive to each of sultamicillin, cefuroxime, ceftriaxone and ceftazidime, 7.7% of *Strept. pneumoniae* were resistant to crystalline penicillin, 6.7% to ampicillin, and 69.2% to chloramphenicol; one of the two *H. influenzae* isolates was chloramphenicol-resistant. Amongst the 30 (42.3%) fatal cases, the length of stay was significantly shorter in GNB-positive cases ($P = 0.045$). Mortality was significantly higher amongst cases with purulent/turbid CSF at admission ($P = 0.03$), and in those with CSF protein of >150mg/dl ($P = 0.02$) and glucose <1mg/dl ($P = 0.047$). The present aetiological preponderance of GPC and *Strept. pneumoniae* in our study population, the high case-fatality, and the emerging resistance profile suggest the need for exploring additional control options including vaccination. We emphasize the need for periodic auditing of local antimicrobial policies in CPM.

Keywords: *Childhood bacterial meningitis; Streptococcus pneumoniae ; Antimicrobial sensitivity ; Empirical therapy ; Ilorin, Nigeria.*

Résumé

La thérapie empirique antimicrobial reste justifiable dans la méningite pyogenique d'enfance (MPE), mais l'éfficacité continue dans une situation particulière, réquise une surveillance microbilogique périodique. C' était ce besoin qui a nécessité l'étude actuelle et retrospective des admissions consecutives de cinq ans au centre hospitalier universitaire d'Ilorin (Nigéria).Parmi les 71 analyses liquides cérébrorachidiens (LCR), 41 (57,6%) étaient positifs en prélèvement-gramme (PPG). Cocci gramme-positifive (CGP) était identifié dans 23 (56,1%) prélèvements, alors que 14(34,2%) avaient Bacilli gramme-négative (BGN). Il n'y avait que 3 (7,3%) avec Diplococci gramme-négative (DGN). En dépit des découverts biochimiques corroboratives, le rest 30(42,3%) y comprennent deux malades de méningite tuberculaire, avaient démontré négatif en prélèvement. Les cas de CGP avaient une moyenne âge de 4,49 ± 5,3 ans. BGN, 3,06 + 4,8 ans et DGN, 4,47 + 4,9 ans, les isolés de LCR sont faits dans 28 (39,4%) cas. *Streptococcus pneumoniae* était responsible pour la majorité de 22(78,6%) (p= 0,00), *Haemophilus influenzae* pour 2(7,1%) et *Neisseria meningitidis* pour 1 (3,5%) cas seulement. Alors que les isoles *Strept. pneumoniae* et *H. influenzae* étaient uniformement sensiblent à sultamicilline, cefuroxime ceftriaxone et ceftizidime, 7,7% de *Strept. pnuemoniae* avaient une résistance à *Crystalline penicilline*, 6,7% à l'ampicilline, et 69,2% au chloramphenicol. Parmi les 30 (42,3%) cas graves, la durée d'attente était plus significativement court que dans les cas de BNG-positif (p=0,045). La mortalité était plus singificativement élévée parmi les cas LCR purulent/turbide au point d'admission (p=0,03), et dans ceux qui ont protéine LCR du >150mg/dl (p=0,02) et glucose de < 1mg/dl (p=0,047).La fréquence étiologique actuelle de CGP et *Strept. pneumoniae* dans notre population d'étude, Un cas mortel élevé, et le profil de résistance emergante suggèrent le besion d'explorer des options de contrôle supplementaire dont comprennent la vaccination. Nous mettons l'accent sur le besoin pour une vérification des politiques locales antimicrobiales en MPE.

Introduction

The last 3-4 decades of the antibiotic era have undoubtedly witnessed a tremendous decline in the case fatality rates of most infectious diseases [1,2] Despite the related dramatic improvement in the prognosis of bacterial meningitis, the corresponding decrease in disease morbidity and mortality in children, has however remained modest [2]. Indeed, up until the recent introduction of the *Haemophilus influenzae* type b (Hib) conjugate vaccine, morbidity reports [3-5] had suggested an increasing morbidity and mortality burden of some specific childhood bacterial meningitides (CBM). Against the background of the well-known inadequacies in the health-care system of most resource-poor third world countries, [6-8] the emergence of disease pathogens resistant to erstwhile cost-effective antimicrobials [9,10], the well known intermittent epidemics in sub-Saharan Africa [10,11], inter-community differences and temporal changes (even within the same geographical boundaries) [12-15], as well as conceivable differences in access to "over-the counter" antimicrobials between urban and rural communities, the current audit of the microbiological characteristics of CBM in our locality was considered long overdue. Furthermore, for a potentially fatal disease like CBM, the need for periodic validation of the continuing sensitivity of the causative pathogens to antimicrobials in use is particularly imperative in a country where the subsisting inadequacies of investigative modalities often compel the clinician to continue the initial "blind" antimicrobial(s) for the entire

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treatment course. With these in mind, the present study was undertaken to characterize and determine the sensitivity patterns of the causative agents of bacterial meningitis in cases admitted to the Emergency Paediatric Unit of a tertiary care Nigerian health facility - the University of Ilorin Teaching Hospital, Ilorin. It was also envisaged that the study outcome would provide the needed scientific impetus for a subsequent prospective study.

Patients and methods

Background data on the inception cohort and hospital

The present communication is predicated on a five-year retrospective study (January 1992 - December 1996) of consecutive admissions for pyogenic meningitis. The study site was the Emergency Paediatric Unit (EPU) of the University of Ilorin Teaching Hospital (UITH), Ilorin. UITH is a tertiary health facility, but like many other tropical tertiary facilities, it also sub-serves a substantial primary care function to the immediate community. The 20-bedded EPU receives referrals from the General Out-Patient Department of the hospital, private hospitals and (the few) district health facilities within the Ilorin metropolis. A few referrals trickle in from the neighbouring states of Oyo, Osun and Ekiti in southwestern Nigeria, as well as from Sokoto, Kogi and Niger states, all of which like Ilorin lie within the Guinea-Savannah zone. This zone encompasses the well-known meningococcal belt of sub-Saharan Africa.

Methodology

Children with a discharge or post-mortem diagnosis of pyogenic/bacterial meningitis were first identified from the admission register. The individual case records were then retrieved for the purpose of extracting the following data:

i) Microbiologic and biochemical parameters of the lumbar puncture cerebrospinal fluid (CSF) at admission that were adjudged consistent with a clinical diagnosis of pyogenic/bacterial meningitis as defined earlier. [13,16] These included, CSF leucocytes, Gram-Smear results, culture isolates and their sensitivities, CSF protein and glucose, and in some cases, the concomitant random blood sugar. The CSF bacteriology data in the case notes were each verified from duplicate records in the Microbiology department. (ii) Relevant demographic and clinical parameters, including the presence of neurologic deficits and other short-term complications. In those with fever and /or coma, the pre-admission duration and the resolution times were also documented as available in the case records. The clinical correlates of the major aetiological categories constitute the subject of a forth coming communication. (iii) Haematocrit, total white blood cell (WBC)}, and differential counts, as well the heamoglobin geno type, and the electrolytes as available. (iv) Outcome variables comprising one of "death", "survival" or "discharge against medical advice". The duration of hospital stay for survivors and fatal cases were also recorded for each patient.

The CSF specimens and blood samples were processed and analyzed as routine samples using standard laboratory techniques [13,16].

Treatment

Empirical antimicrobials were chosen in accordance with the institutional guidelines for CPM. These comprised one of either a combination of benzyl penicillin and chloramphenicol, or ampicillin and chloramphenicol. Monotherapy was however pursued on receiving the relevant microbiologic data.

A few were treated from the onset with, or changed to one of cefuroxime, ceftazidime, ceftriaxone or sultamicillin [unasyn®]} either because of poor clinical response and/or lack of CSF sterilization after 48-72 hours of empirical therapy, or on account of a long pre-hospitalization symptom-duration. Each patient had standard supportive care [13,16] In-patient treatment lasted 10-14 days, or ≥ 72 hours after defervescence, which ever was longer. At discharge, many subjects were weaned to the appropriate oral antimicrobials.

Data Analyses

Using the *EPI-INFO 6* software package of a microcomputer, the clinical and microbiologic data were entered, cross-tabulated and subsequently analyzed for statistical significance, using one of *chi-square test* {with or without *Yates' or the Mantel-Haenzel* correction}, or *the Fisher's Exact test* as appropriate. The 95% confidence intervals (95%CI), odds' ratio (OR), and relative risk (RR) were obtained as applicable. Mean values were compared using the well-known analysis of variance (ANOVA) test. Significant associations was presumed if $P < 0.05$.

Results

Over the study period, there were 9,603 EPU admissions. Of these, a clinical diagnosis of pyogenic meningitis was supported by corroborative CSF findings in 71 cases {including two cases with tuberculous meningitis [TBM]}. Thus, the estimated hospital prevalence of paediatric bacterial meningitis was 7.4 per thousand. As shown in Figure 1, the trend line for meningitis admission (unlike the trend for the overall EPU admissions),

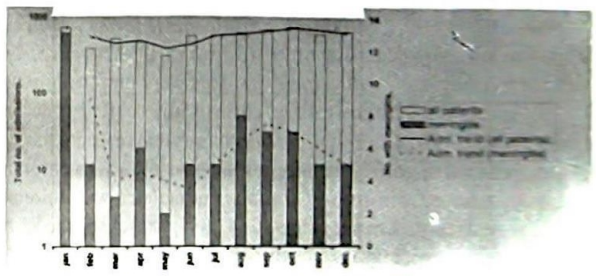

Fig. 1: Monthly emergency paediatric unit's admission (1992-1996) for all patients, vis-a-vis those with pyogenic meningitis. Note the admission trend indicating a peak admission for meningitis between August and January, and an abrupt trough in February throug May.

suggests a preponderance of cases between August and February of every year, with a transient rise in April. This trend coincided with a peak prevalence in the dry, but cool-and-dusty harmattan stretch (September–December), and the ensuing hot dry season which usually ends by May/June. The same seasonal trend was observed in the frequency of pathogen identification, and Gram-smear positive cases.

Demographic parameters and CSF microbiologic variables

The 71 cases comprised 43 males and 28 females, and hence the male: female (M:F) ratio of 1.5:1. Thirty-seven (52.1%) cases were aged 2 months-5 years, while 12 (16.9%) were ≤ 2months old at presentation; 14 (19.7%) were school-aged children above five years, including seven cases aged 11-16 years. Demographic data were incomplete in the remaining eight (11.2%) cases. With

regard to the lumbar CSF characteristics, a laboratory confirmation of the parameters documented in the case-record was obtained in 31 cases. Eighteen (58.1%) of the 31 cases (in whose case records the relevant data were available) had a turbid CSF, while 6 (19.4%) others were recorded as purulent. The CSF appearance was recorded as xanthochromic in three (10.7%) cases, while four (12.9%) others had a clear and colourless CSF. Forty-one (57.8%) cases whose CSF smear was positive after Gram staining were categorized as Gram-smear positive [GSP]. Thirty others (56.3%) whose CSF Gram-smear proved negative, but whose clinical and/or CSF biochemical parameters were otherwise suggestive of pyogenic meningitis were categorized as Gram-smear negative (GSN); 2 of these had erstwhile features of TBM. Of the 28 non-TBM cases in the GSN category, a clear and complete documentation of the lumbar CSF appearance was available in 16 cases. In 11(68.8%) of these, the CSF was visibly purulent or turbid. A similar observation of an infected CSF (i.e. a purulent or turbid appearance) was made in 17(70.8%) out of the 24 GSP cases with complete CSF macroscopy data. The relative prevalence of a purulent/turbid *vs.* xanthochromic/clear CSF was comparable between GSN and GSP cases *(P=1.0,* 2-tailed FET). Similarly, amongst GSP cases there was no statistical difference in the distribution of a visibly infected CSF (purulent/turbid), between the GPC and GNB categories *(P=0.64, 2-tailed FET).*

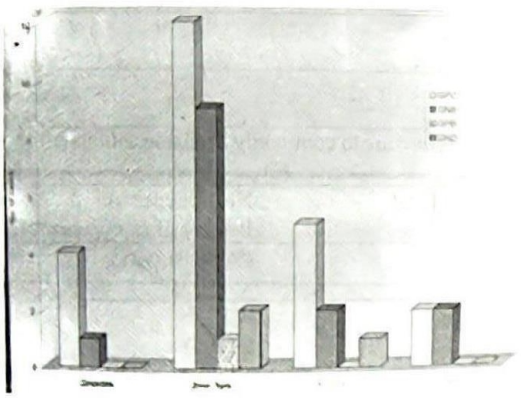

Fig. 2a: Gram-smear categories of cases of pyogenic meningitis according to age groups. The gram-smear distribution was not significantly different between the age groups (P = 0.63; X^2= 0.91).
GPC = Gram-positive cocci
GNB = Gram-negative bacilli
GPB = Gram-positive bacilli (which yielded aerobic spore bearers on culture)
GND = Gram-negative diplococci

Figures 2A and 2B show the age-related distribution of the Gram-smear categories, and the CSF (culture) isolates amongst smear-positive cases. Gram-positive cocci (GPC), accounted for 23 (56.1%), Gram-negative bacilli (GNB) for 14 (34.2%), and Gram-negative diplococci (GND) for only 3(7.3%) cases. Gram-positive bacilli were identified from the CSF of an infant whose CSF culture ultimately yielded aerobic spore bearers. The latter was however disregarded as contaminants in the subsequent analyses. The mean ages for GSN and GSP cases were 2.6 yrs (SD, 2.9;n =25) and 3.95 yrs(SD, 5.0;n = 41) respectively. For the GPC category, the mean age was 4.49 yrs (SD, 5.3; n = 23), while the GNB and GND categories recorded mean ages of 3.15 yrs (SD, 4.8; n = 14) and 4.47 yrs (SD, 4.9; n = 3) respectively. There was no significant difference between the mean ages of GSN and GSP cases, *(P*=0.25; F-Statistics=1.37). Similarly, the mean ages of cases in the GPC, GNB and GNC categories were comparable *(P* = 0.73;F-Statistics=0.31).

With regard to the distribution of the isolates in the 28 culture-positive cases (Figure 2B), *Streptococcus pneumoniae* accounted for a predominant 22 (78.6%) of the CSF isolates, *Haemophilus influenzae* for two (7.0%) cases, and *Neisseria meningitidis* for one (3.6%). *Klebsiella* species was isolated in two cases, including a 12-day old infant, while *Staphylococcus aureus* proved the eventual isolate in an 11-year year old with impetiginous skin lesions and bilateral suppurative otitis media. Although the overall proportion of *Strept. pneumoniae* isolates was significantly higher *(P=0.00),* the CSF isolates were not significantly different between the age-group categories (P = *0.40;* X^2=*1.85*) {Fig. 2B}.

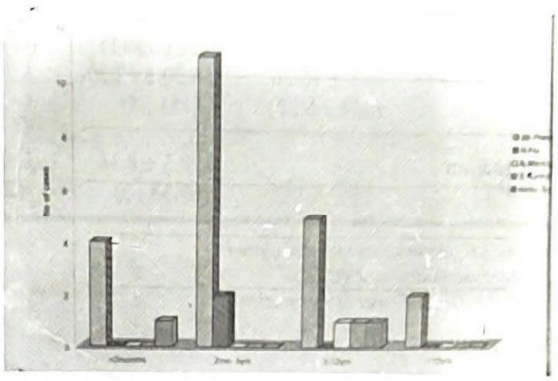

Fig. 2b: Cerebrospinal fluid bacterial isolates in infants and children according to Age groups. Note the preponderance of *Streptococcus pneumoniae* isolates in all age groups, including young infants, aged < 2 months. Isolates were however not significantly different between the age categories (P = 0.4, X^2=1.85)
Str. Pneum. = Streptococcus pneumoniae; H. Flu = Haemophilus influenzae; N. Mening. = Neisseria meningitis; S.Aureus = Staphylococcus aureus; Klebsiella spp. = Klebsiella species.

Selected laboratory parameters in relation to aetiologic categories

Table I shows the distribution of selected CSF characteristics, haematological parameters, as well as the serum sodium, in relation to the Gram-smear categories. Whilst the highest mean values for CSF protein, and the lowest for CSF sugar were recorded in the GPC category, neither of these parameters differed significantly between the Gram-smear categories (Table I). Similarly, despite the apparently lower mean haematocrit value in the GSP categories, the mean haematocrit and other haematological parameters did not differ significantly between smear-positive (GSP) and smear-negative (GSN) cases. Similarly, these same parameters were comparable for the GPC and GNB categories. However, the small sample sizes of some of the CSF culture isolates of specific bacterial agents (especially *H. influenzae* and *N. meningitidis*), precluded a similar comparison of these laboratory parameters between the three major categories of bacterial isolates.

Sensitivity patterns of CSF bacterial isolates

Table II shows the sensitivity patterns of *Strept. pneumoniae* and *H. influenzae* to some selected antimicrobials. The sample sizes of *H. influenzae* and *N. meningitidis* were however limited, as were the spectrum of the relevant disks available. Twelve

Table 1: Selected investigative parameters, according to CSF gram-smear results.

	Partially treatd/ GSN Mean ± SD (Variance ; n)	GPC Mean ± SD (Variance ; n)	GNB Mean ± SD (Variance ; n)	GND Mean ± SD (Variance ; n)	GSP Mean ± SD (Variance ; n)	p-value t GSN vs GSP[GPC vs GNB vs GNC]
CSF Biochemistry						
Mean CSF protein	195.4 ± 167.79 (28154.93 ; 10)	280.1 ± 300.36 (90218.98 ; 15)	188 ± 50.99 (2600 ; 6)	176.5 ±109.6 (12012.5 ; 2)	247.30±246.4 (60713.8 ; 23)	0.55 [0.69]
Mean CSF Glucose	2.15 ± 1.24 (1.54 ; 8)	1.28 ± 1.34 (1.79; 12)	2.23 ± 1.23 (1.50; 7)	-	1.763 ± 1.44 (2.08 ; 20)	0.51 [0.13]
Haematological parameters:						
Packed cell vol. (PCV)	31.88 ± 6.36 (40.41 ; 8)	24.7 ± 5.85 (34.23 ; 10)	30.6 ± 6.91 (47.8 ; 5)	–	26.4 ± 6.91 (47.69 ; 15)	0.07 [0.10]
Total WBCx10/L	7.75 ± 4.08 (16.64 ; 6)	10.55 ± 4.58 (21.00 ; 11)	11.3 ± 6.79 (46.15 ; 4)	-	11.3 ± 5.3 (28.13 ; 16)	0.15 [0.8]
% Polymorphs*	75.5 ± 16.26 (264.5 5 ; 2)	66.50 ± 12.29 (151 ; 4)	-	-	73 ± 17.22 (296.5 ; 5)	0.86 [~]
Others						
Serum sodium	-	120.3 ± 8.33 (69.33 ; 3)	130 ± 4.62 (21.33 ; 4)	–	130 ± 4.62 (21.33 ; 4)	~[0.88]

**Only mean percentages are compared.*
tStatistical method was ANOVA.
See text for Gram-Smear abbreviations.

Table 2: Sensitivity patterns of *Streptococcus pneumoniae* and *Haemophilus influenzae* to commonly available antibiotics.

Antibiotic	Total Tested. *S. pneum.*	No of Sensitive Isolates of *S. pneum.* (% Sensitivity)	Total tested *H.infl.*	No. of Sensitive Isolates of *H. influenzae* (% Sensitivity)
Xtalline penicillin	13	12 (92.3)	NT	NT
Ampicillin	15	14 (93.3)	2	2 (100)
Chloramphenicol	13	4 (30.8)	2	1 (50)
Cloxacillin	8	8 (100.0)	NT	NT
Gentamicin	5	2 (40.0)	NT	NT
Sulbactam/Ampicillin	4	4 (100)	1	1 (100)
Cefuroxime	4	4 (100)	1	1 (100)
Ceftazidime	2	1 (100)	1	1 (100)
Ceftriaxone	2	1 (100)	1	1 (100)
Erythromycin	13	13	2	2 (100)

NT = Not tested

(92.32%) of the 13 isolates of *Strept. pneumoniae* were reportedly sensitive to crystalline penicillin, while the corresponding sensitivities to ampicillin and sultamicillin (a beta-lactamase stable sulbactam-ampicillin combination available locally as Unasyn®) were 93.3% and 100%, respectively. However, none of the *Strept pneumoniae* tested proved resistant to each of cefuroxime, ceftriaxone and ceftazidime.

As regards the two *H. influenzae* isolates, the sensitivity pattern suggests a relative preservation of the efficacy of ampicillin, but resistance to chloramphenicol was reported in one of the two isolates (Table 2).

Admission outcome in relation to demographic/clinical and CSF microbiologic parameters:

Excluding the nine who had discharge against medical advice, 30 (48.4%) deaths were recorded amongst the remaining 62 cases. As shown in Table 3, the highest age-specific case fatality rates of 58.9% and 75% were seen in children aged 2 months - 5 years and those >12 yrs respectively. For children aged < 12yrs the age-specific case fatality was not significantly different between the three age group categories compared ($P = 0.19$). Similarly, the gender distribution of fatal cases and disease-survivors were comparable ($P = 0.65$).

With regard to the microbiologic parameters, a turbid or purulent CSF at the first lumbar puncture was associated with a significantly higher mortality, compared with a xanthochromic or clear fluid (Table 3). Fifteen (62.5%) of the 24 with a turbid or purulent CSF died, as against only one (14.3%) of 7 cases whose CSF was clear or xanthochromic at admission ($P = 0.03$, $OR = 0.10$; $95\%CI = 0.00\text{-}1.10$). As shown in Table IV,

Table 3: Selected clinical and investigative parameters according to admission outcome in infants and children with pyogenic meningitis.

Parameters	Admission Outcome						*P*-value.
	Survived	Died	DAMA	Total	No. assessed	% Mortality	
a) *Demographic parameters*:							
Age:							
<2m	8	4	-	12	12	33.3	
2m-5yr	14	20	5	39	34	58.9	
5.12yrs	9	3	4	16	12	25.0	0.19
>12yrs	1	3	-	4	4	75.0	
Gender:							
Male	21	18	4	43	39	41.8	
Female	11	12	5	28	23	42.0	0.65
b) *CSF Appearance(n=31)#*							
Turbid	8	10	3	21	18	55.6	
Purulent	1	5	-	6	6	83.3	
Xanthochromic/Bid-stained	2	1	-	3	3	33.3	0.3§
Clear & Colourless	4	-	-	4	4	0	
Unknown	15	13	9	37	-	45.2	
c) *Gram-Smear Categories*:							
Gram-smear Neg (GSN)	12	14	2	28	26	53.9	
Gram-positive diplococci	11	9	3	23	20	45.0	
Gram-negative bacilli	9	3	2	14	12	25.0	3.30 (0.35)
Gram-negative diplococci	1	2	-	3	3	66.7	
Gram-positive bacilli	1	-	-	1	1	0	
GSN with TB meningitis	-	1	1	2	1	100	
d) *CSF isolates*							
Strept. pneumoniae	10	9	2	21	19	47.4	0.28
H. influenzae	2	-	-	2	2	0	-
N. meningitis	-	1	-	1	1	100	-
Others	3	-	2	5	2	0	-
e) *CSFiochem. (mg/dl)##*							
CSF Protein(mg/dl):							
<150	7 {9}	{2]	{1}	7 {12}	7 {11}	0 {18.2}	0.02§
>150	6 {9}	7{10}	3{4}	16 {23}	13{19}	53.9{52.6}	{0.07}
CSF Sugar (mg/dl):							
<1	3 {4}	4 {4}	{1}	7 {9}	7 {8}	57.1 {50.0}	0.047§
=1	5 {7}	{3}	2{3}	7 {13}	5 {10}	0 {33.3}	{0.39}

 # For statistical analysis, values in the "Turbid" and "Purulent" cells are pooled, as well as the "Xanthochromic/blood stained" categories with those of the "Clear and Colourless" ; Gram-Positive Bacilli and GSN with TB meningitis excluded from analyses
•Refers to discharge against medical advice, and hence had incomplete data record.
Attributable to incomplete documentation of CSF parameters; excluded from statistical testing
##Represent values for smear-positive cases only; Values inclusive of GSN cases including p-values" are indicated in bold parentheses.
§Significant difference(s) shown in the distribution; Fisher's Exact values were 0.07 and 0.35 respectively for "row <1" and "row>1" mg/dl of CSF sugar.

neither the (CSF) Gram-smear category, nor the ultimate culture isolates, correlated significantly with the admission outcome. Whilst as many as 14(53.9%) of the 26 GSN cases proved fatal, amongst smear-positive cases, the highest (smear-specific) mortality of 45.0% was seen in the GPC category. A corresponding value of 47.4% was recorded in the *Strept. pneumoniae* category. Although, neither of the two with *H. influenzae* isolates proved fatal, the mortality rate for the GNB category was 25%. Amongst those with GND smears, 2 cases including a 10year old whose CSF grew *N. meningitidis*, proved fatal (Table 3).

As regards the CSF biochemical parameters, all seven smear-positive cases whose CSF protein was above 150 mg/dl proved fatal, as against six (46.2%) of the 13 amongst survivors. On the other hand, none of the four fatal GSP cases had a CSF sugar above 1 mg/dl. Each of a CSF protein of >150mg/dl, and glucose <1mg/dl appeared to portend a fatal outcome of admission *(P = 0.02 & 0.047* respectively) (Table 3).

Table 4 shows the relationship between the duration of hospital stay (in survivors and fatal cases), and the Gram-smear categories. Whilst the duration of hospital admission in survivors was not significantly related to the Gram-smear categories, fatal cases in the GNB category stayed for a significantly shorter time before demise, than their peers in the GPD category *(P=0.04, Fisher's Exact Test)*.

Discussion

The local morbidity burden of paediatric pyogenic meningitis as reflected by an estimated hospital prevalence of 7.4 per 1000

Table 4: Duration of hospital admission in survivors and fatal cases of pyogenic meningitis according to Gram-smear categories

	Gram - Smear Categories						*P*-value¶
	GSN	GSP	GPD	GNB	GND	Others (GPB)	GSN vs GSP (GSP vs GNB/vsGNC)
Survivors:							
Mean	12.64	16.67	16.45 5.11	16.44	21	-	0.14 (0.96)
SD	4.84	8.10		11.36			
Variance	23.45	65.63	26.1	129.03 9	~	~	
n	11	21	11		1	~	
No. of Days							
≤ 16	9	14	8	6	0	~	0.38 (0.57)
> 16	2	7	3	3	1	~	
DAMA	4	5	2	2		1	
Deaths							
Mean	4.99	2.8 2.2	3.72 2.31	1.67	0.63	~	
SD	8.33			0.58	~		0.37 (0.11)
Variance	69.35	4.96 14	5.32	0.33	~	~	
n	12		9	3	2	~	
No. of Days							
≤ 2	6	7	2	3	2	~	0.69 (0.045) §
> 2	6	7	7	0	0	~	
Unknown #	2	2	2	~	~	~	

Statistical testing with one of ANOVA, Yates' or Mantel-Haenszel corrected chi-square or Fisher's Exact Test as appropriate
DAMA = Discharge Against Medical Advice; Comprised 9 cases with whom the patients either absconded, or insisted on leaving despite medical advice to the contrary
§ Significant difference found for the cells compared
 # Attributable to incomplete documentation; excluded from statistical analyses.

admissions in the current study is conceivably an underestimation. As earlier remarked by Schucat and Wenger [10], such under-representation is not unusual in a community where the inter-facility referral system is poorly organized, and the cost of health care (and its affordability by patients) determines the utilization of health-care facilities. Both factors subsist in our setting. Other contributory factors included the exclusion for logistic reasons of some cases of neonatal meningitis managed at our remotely located NICU (some 9 km from the EPU), as well as a similar exclusion of young adolescents supervised at the adults' emergency unit. Despite these, and the usual limitations of a retrospective study, the present series, lived up to the anticipated provision of a clinical and laboratory database for rational therapeutic recommendations on paediatric pyogenic meningitis.

The dry seasonal/harmattan peak is consistent with the observations in some earlier series from West and Central Africa [17-20]. An earlier repot [17] had attributed the preponderance of cases during the dry, cool-but-dusty harmattan to a conceivable surge in mucosal cracks of the upper respiratory tract and a consequent blood invasion by droplet-acquired nasopharyngeal pathogens. Similarly, the high ambient temperature and low humidity during the hot dry season would conceivably account for an enhancement of droplet-acquired upper respiratory infections [21]. The current observations regarding disease seasonality, as well as the identification of the highest morbidity and mortality burden in the under-five constitute a potentially useful epidemiological database for future preventative programs (including vaccination) in the West African subregion.

Against the background of the awesome morbidity and mortality profile of bacterial meningitis [10,21-23] and the subsisting inadequacies of appropriate laboratory support in many tropical health facilities, a prompt initiation of appropriate empirical antimicrobials (based on the prevailing microbiological data), remains the rational option for disease control. In this regard, the current identification of GPD/*Str. Pneumoniae* in over two-thirds of cases, is noteworthy for the therapeutic import of its striking difference from some earlier regional series [6,8]. In the earlier report from Zaria [8] (a city which is reputed not only for its intermittent epidemic meningococcal meningitis, but comparable with Ilorin in the climatic characteristics and semi-urban setting in central (middle-belt) Nigeria), pneumococcus accounted for only 11% of cases. Our findings are however in accord with those of some earlier regional series, including recent reports from south-western Nigeria [6,11,22,23] That a significant preponderance of *Strept. pneumoniae* was identified in the present series, is conceivably related to a soaring antimicrobial resistance pressure. This may in turn be partly attributed to an increasing resort to antimicrobial self-medication/inappropriate prescription pattern in urban/semi-urban settings. Also, the continued local subsistence of some risk factors of nasopharyngeal acquisition of pneumococcus (like urban-slum overcrowding and poor ventilation [10,13]), as well as, the sizeable population of children with sickle cell disease (who are reportedly more susceptible to invasive pneumococcal diseases [10,13]) may also be contributory. On the other hand, and in contrast to earlier reports [6,21] the paucity of *H. influenzae* isolates in the present series was rather surprising, more so in

view of the preponderance of the vulnerable under-five children [10-13] However, even in the absence of an organized preventive programme, recent reports from the African region [22-25] suggest that invasive *H. influenzae* diseases are uncommon. While laboratory constraints may arguably account in part for the current paucity of this admittedly fastidious agent, it is our view that pre-consultation antibiotic abuse constitutes the more plausible explanation. The possible validity of this explanation is buttressed by the frequent abuse of ampicillin and chloramphenicol (both of which had shown varying efficacy against *H. influenzae*) for treating presumed typhoid fever in febrile children who fail to respond to simple antimalarial medication(s). Against the background of possible laboratory inadequacies, as well as the present sizable proportion of partially treated (GSN) cases, there is a dire need for exploring cost-effective, but rapid diagnostic options. Such options include the counter-current immuno-electrophoresis (CIE), enzyme-linked immunosorbent assay (ELISA), or the latex agglutination tests (LAT) [9,13,26]. The propensity of the GNB category (amongst whom only two cases proved *H. influenzae* positive) for fatality within a significantly shorter time than other Gram-smear categories, and the reported utility value of LAT in a recent Ghanaian report [18] underscore the urgency of the local need for exploring the usefulness of more sensitive diagnostic techniques.

The local rarity of meningococcal meningitis despite the geographical location of Ilorin within the well known meningococcal belt [8,10], underscores the reality of temporal changes in microbiologic data (and hence the need for periodic auditing), even within the same national boundaries [13, 27] Possible explanations include the zeal with which the local anti-meningococcal immunization campaign had been pursued following the last (mid-decade) devastating meningococcal epidemic in Northwestern Nigeria. This putative immunization-related wane in meningococcal disease, coupled with the "success story" recorded in recent Hib-vaccination trials [10,27,28] constitute valid grounds for exploring similar vaccine-prevention strategies for the more locally relevant (and frequently fatal) pneumococcal meningitis. The efficacy of the 23-valent pneumococcal vaccine in children above 2 years, and the elderly (>65 years) has been documented [27,29-31] but concerns about its immunogenicity in infants [27] had led to the development of a pneumococcal polysaccharide conjugate vaccine, similar to the Hib conjugate vaccine. While we await the validation of the efficacy of this new pneumococcal conjugate vaccine [27], the high case fatality of pneumococcal meningitis underscores the dire need for initiating additional control measures. Furthermore, the local reality of a sizable population of vulnerable children with sickle cell disease (SCD) (two of whom had fatal pneumococcal disease in this series) constitutes another compelling reason. Selective chemoprophylaxis of such at-risk children [13,27] is one of such measures. Others include enforcing better housing standards [13,27], as well as evolving national guidelines on rational use of antimicrobial agents to reduce the risk of nasopharyngeal carriage of resistant organisms.

The identification of *Strept. pneumoniae,* rather than Group B Streptococcus [GBS] as the predominant Gram-positive agent in neonatal meningitis, despite significant maternal vaginal colonization [14,34,35] is noteworthy in view of its concordance with earlier reports [14,23,33] While this contrasts with the experience in western countries [3,9,10] the identification of *Klebsiella* spp. as an important Gram-negative pathogen of neonatal meningitis in the present series was hardly surprising in view of similar observations in previous local series [36,37] Hence, the subsisting empirical combination of ampicillin and gentamicin for neonatal meningitis should provide adequate coverage not only for this agent, but also for *Strept. pneumoniae,* and perhaps an unsuspected *Listeria monocytogenes.* However, the present reality of invasive pneumococcal disease in the newborn, the emerging resistance pattern of this agent to ampicillin [38], as well as the possibility of a *Staph. aureus* sepsis [14,32,33,35,36] (for which the beta-lactamase "naïve" ampicillin is ineffective) would favour the choice. Given the reportedly superior pneumococcal coverage of sultamicillin, when compared with ampicillin [39], the current sensitivity patterns appear to favour our endorsement of a combination of sultamicillin (a beta-lactamase stable ampicillin-sulbactam combination) and gentamicin as the alternative initial antimicrobials for neonatal meningitis. The comparatively cheaper cost of sultamicillin makes it a better choice over the more expensive third generation cephalosporins.

The limited sample size of the sensitivity/resistance data would obviously preclude firm conclusions on the therapeutic import(s) of the patterns in the present series. Despite the few cases of pneumococcal resistance to penicillin, a change in the current local empirical recommendations would probably need to await the outcome of a larger series, preferably a prospective study. Penicillin-resistant pneumococcus had been reported elsewhere, in Africa [40,41], but the current low prevalence of pneumococcal resistance, as well as its concomitant coverage of meningococcal disease, constitute additional grounds for its continued therapeutic relevance in Nigeria. Also cost considerations would favour the choice of this agent in our setting, where parents still bear the cost of paediatric care. However, given the emerging trend of an increasing resistance of *Strept. pneumococcus* to crystalline penicillin [38] and *H. influenzae* to chloramphenicol [42], in children older than 2 months, there is clearly a need for exploring alternative empirical therapeutic options to the current first line combination of benzyl penicillin and chloramphenicol. As shown by the present study, the sensitivity profile of sultamicillin as well as its documented efficacy against a possible meningococcal disease [43], should favour its choice over the equally efficacious but more expensive third-generation cephalosporins. The latter agents may however be reserved as second line drugs. Although the second-generation cefuroxime is an equally cheap option, but its slow CSF sterilization, and hence the propensity for disease relapse [13] would weigh against its endorsement. Finally, against the background of the under-funded health-care system of most tropical countries, and the recent report from Barcelona, Spain [44] where chloramphenicol-resistant *H. influenzae* disease accounted for 50% of cases, there is an urgent local need for pre-emptive institutional and national policies on the rational use of antimicrobial agents.

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