Nigerian Journal of Clinical Practice
Sept 2008 Vol 11(3) :235-245

NEONATAL BACTERIAL MENINGITIS AND DEXAMETHASONE ADJUNCTIVE USAGE IN NIGERIA

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ABSTRACT

Objective: Neonatal bacterial meningitis is devastating, with attendant high mortality and neurological sequelae. We, therefore, aimed to delineate its current incidence, etiologic, clinical, laboratory spectra, and the effect of steroid therapy on the outcome.

Methodology: Babies admitted from1992 to 1995 in the Special Care Baby Unit of the University of Maiduguri Teaching Hospital, Maduguri, Nigeria, with bacterial meningitis were studied prospectively. Neonatal bacterial meningitis was confirmed if the cerebrospinal fluid (CSF) microbiological, chemical, immunological and clinical criteria were satisfied. Detailed neurological follow-up was made.

Result: Sixty-nine cases of neonatal bacterial meningitis were encountered, (25 were early-onset, and 44 late-onset); the incidence was 6.5/1000 live births. 22 Positive CSF cultures were grown in early-onset meningitis, and 28 in late-onset disease. Low birth weight showed higher risk of bacterial meningitis and it was significantly more likely in the preterm. X^2=24.19, p = 0.000001). Gram-negative pathogens were more isolated (28/50, 56%); *Escherichia coli* (11) being the commonest, while of the Gram-positive pathogens *Staphylococcus aureus* was most predominant overall (13/50). Concomitant blood culture was positive in 39/50 (78%), inclusive of all 22 "definite" early-onset disease. The CSF WBC was minimally raised (25-30 x 10^6/L) in 11 (22%) of "definite" neonatal bacterial meningitis. Detection of unusual pathogens was noteworthy: *N. meningitidis* (2) and *H.influenzae* (2), contributing 0.6 and 2.2 per 1000 live births and admissions, respectively. Overall mortality was 24.6%. Of the forty survivors, 9(22.5%) had neurological sequelae: sensorineural hearing deficit (3), hydrocephalus (2), subdural effusion (2), hemiparesis (1), afebrile (recurrent) seizure (1), and there was reduced developmental quotients at 24 months follow-up in 33. Dexamethasone therapy decreased mortality significantly; p = 0.0004.

Conclusion: The new information highlighted by this research includes the lack of Group B Streptococcus isolation, the finding *of S. pneumoniae, N.meningitidis, H.influenzae and S. aureus* as significant pathogens, usefulness of blood cultures in the detection of neonatal bacterial meningitis, increasing resistance of Gram-positive neonatal pathogens to cloxacillin, low CSF WBC, and the finding that the adjunctive use of dexamethasone significantly decreases case fatality and neurological sequelae.

Key Wards: Neonatal, Meningitis, Dexamethasone *(Accepted 9 August 2007)*

INTRODUCTION

Neonatal bacterial meningitis is a troublesome and life-threatening infection that a newborn and the family can encounter. Despite advancements in its treatment over the past 50-60 years, mortality remains high at between 25 to 50 percent.[1-4] Neurological sequelae are common among survivors with involvement of more than 25% and up to 41% documented.[3-4] Furthermore, 6-12% hearing impairment has been suggested.[5]

Evaluations based on a geographically defined population in the USA have shown rates of 0.2 - 0.5 cases of bacterial meningitis per 1000 live births.[6] Reviews from Europe and Australia show similar rates but with particularly high rates of 0.7 - 1.9 per 1000 reported for the African continent.[1-4, 7-9]

There is evidence that the incidence is on the increase with a changing trend in the causative organisms in some communities.[10] Group B streptococci (GBS) and *Listeria monocytogenes* are common in the developed world/affluent societies.[2, 9, 11-13]

With the continuing scourge of neonatal infections, particularly bacterial meningitis, we felt it necessary to prospectively study our neonates over a 4-year period in the Special Care Baby Unit (SCBU), of the University of Maiduguri Teaching Hospital (UMTH), Maiduguri, Nigeria. The study set out to determine the current incidence of neonatal bacterial meningitis, its etiological, clinical and laboratory

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spectra, and ascertain the neurodevelopmental outcome. As a corollary, and in view of the suggestions on the effects of steroids on bacterial meningitis, [2, 14-16] the usefulness or contribution to outcome of dexamethasone was also assessed.

PATIENTS AND METHODS

All babies with definite or probable meningitis were recruited and studied prospectively over the said period (1992 to 1995) in SCBU of the UMTH, Nigeria. The newborn infants had their gestational ages assessed by using the Dubowitz *et al* scoring system.[17] The UMTH, a centre of excellence for immunology and infectious diseases, is a regional and/or referral hospital which lies within the African "Meningitis belt,"[18] and also serves 3 neighboring countries, Cameroon, Chad and Niger.

Definite neonatal bacterial meningitis was diagnosed if a pure growth of a pathogen was obtained from the primary culture of CSF from a neonate with the clinical picture of meningitis such as seizures, poor feeding, temperature instability and/or stupor. On the other hand, probable neonatal bacterial meningitis was diagnosed if no organism was obtained from primary CSF culture, but the Gram stain was positive or specific bacterial antigen was detected in CSF, and there was a positive blood culture of a neonate with the history or clinical status suggestive of meningitis.

The neonates with suspected sepsis or meningitis were usually investigated for meningitis as previously described, [3,19-20] Cases were diagnosed as neonatal bacterial meningitis if they satisfied any of the five criteria shown below, and as had previously been used:[21]

i) Organism isolated from the *CSF,
Or ii) Positive Gram stain/bacteria seen in CSF,
Or iii) Blood culture positive with no CSF isolate but with signs of CSF anomaly
defined as greater than 100 white cells (mainly polymorphs) x 10^6/L and
CSF protein = 1.5g/1 and CSF glucose < 1.4 mmol/L or < 50% of a [+]simultaneous serum glucose,
Or iv) CSF negative but with CSF pleocytosis and/or disturbance defined as =
200 white cells x 10^6 /L with at least one of the following:
a) CSF protein = 0.75 g/L;
b) CSF glucose < 1.4 mmol/L or < 40% of a [+]simultaneous serum glucose;
c) Specific bacterial antigen detected in CSF; and/or
d) Positive blood culture
Or v) CSF immunodiagnosis; ELISA, Latex agglutination
+Sample that is obtained within 10 minutes prior to performing lumbar puncture

If the CSF obtained was traumatic (blood-stained),a CSF: Blood White cell count (WBC) greater than normal CSF: Blood WBC ratio by 100 cells/mm^3 was also accepted as diagnostic of bacterial meningitis.[3,22] The CSF was taken from the lumbar region following usual standard aseptic technique for performance of lumbar puncture (LP) .

Analysis of CSF in our laboratory was carried out by Gram staining of the centrifuged deposit, WBC count, protein and glucose estimation, as well as standard bacteriological methods of culture, inoculations and identification. All CSF samples were plated onto chocolate agar plate (CAP), and primary bacterial cultures were done by inoculations of deposits on the CAP. These CAPs were of standard characteristics, and adequate CO_2 atmosphere were exposed to all specimens. The species of bacteria were initially identified by their growth and morphology after primary culture or after extended incubation, or following enrichment in cooked meat medium. Strains were speciated and bio-typed according to the method of Kilian[23] and other standard laboratory methods.[24] Plates were incubated aerobically at 37^0C for 18-24 hours. Aerobic spore bearers and other cultures deemed as contaminants were excluded: these included cultures contaminated with spores taken as aerial contaminants and the growth of skin commensals. When in doubt, a new sub-culture of sample was further undertaken. Strict asepsis was observed in culturing these organisms.

Sensitivity of the isolates to antibiotics was determined by the Disc diffusion method, using multidisc sensitivity tests.[25] CSF immunodiagnosis (qualitative detection of specific bacterial polysaccharide surface antigens) was done in some cases using latex agglutination test kit.[26] Viral cultures were not carried out.

All infants with neonatal bacterial meningitis were initially treated empirically according to the Unit's standard policy of gentamicin and cloxacillin intravenously (i.v.) or intramuscularly (i.m.), and later from January 1994, of gentamicin and ceftazidime.[3, 18] The antimicrobial therapy was adjusted according to the laboratory result. Antimicrobial therapy was continued for 14 and twenty-one days for definite Gram-positive and Gram-negative bacterial meningitis, respectively, while treatment for probable cases was given for 10 to 14 days. During the first-half (Phase-1) of the study period, dexamethasone (0.4mg/kg.i.v. bolus, followed with 0.2mg/kg i.v. every 8 hours for 72 hours) was given only as clinically indicated, i.e. when there was a suspicion, or definite evidence of cerebral edema/raised intracranial pressure (ICP). In the second-half (Phase-2) of study period, however, the same dose regimen was routinely used in all alternate cases within one hour of diagnosis, and before or along with the first dose of antimicrobial

irrespective of presence or not of raised ICP; over the same 72 hours duration. Additionally, all cases of raised ICP were concomitantly treated with 20% mannitol therapy at a dose of 1g/kg every 8 hours for 36 hours, at the end of which dexamethasone was still continued.

Although, we concede that this methodologic approach was not the best, it was still worthwhile comparing both phases since other management lines remained unchanged.

Since the Institution had no functional Ethical Committee at the period of study, the Department of Paediatrics gave accent for the study. Informed consent was obtained from all parents. Intrathecal or intraventricular antibiotics was not administered in any newborn infant.

Full neurological and developmental assessments were done regularly in the SCBU, at discharge and at monthly intervals in the follow-up Neonatology Clinic, by one of the authors. The Griffiths Mental Development Scales[27] was used to assess development and the outcome and developmental status of survivor was ascertained, compared and categorized at 24 months of age. More detailed audiological assessment, e.g. brainstem auditory revoked potentials/responses (BAER) was not offered due to lack of facility during period of study. Hearing was, however, assessed by determination of behavioral and orienting responses.[28] A definite hearing disability required four consecutive confirmatory assessments after discharge from the SCBU. Specific adverse risk criteria for the confounding variable of possible congenital hearing loss were clinically reappraised regularly [29, 30] and caused exclusion from analysis.

Statistical Analysis

The Chi-squared test (X^2) and Fisher' exact test using EPI-6 software package were employed where applicable, for differences in which ones as regards incidence, onset and outcome of neonatal bacterial meningitis *vis-à-vis* the use of steroids, with 95% confidence intervals. A *p* value less than 0.05 was taken as significant difference between compared data.

RESULTS

Over the 4-year study period, 4,745 babies were born at UMTH, Maiduguri, Nigeria, out of which 31 babies developed bacterial meningitis. Thus, the incidence of neonatal bacterial meningitis for in-born babies was 6.5 per 100 live births. However, the total SCBU admissions was 1,815, and when the total neonatal bacterial meningitis was reflected, a high proportion of 38.0/1000 was encountered. Thirty-eight babies (out-born with meningitis) were referred from the neighboring hospitals and maternity homes to the SCBU. Also encountered but excluded from analysis were 3 cases that had fungal (*Candida albicans*) meningitis.

There were 25 and 44 cases of early-onset and late-onset meningitis, respectively. Any proven case who is = 72 hours of age and that older than 72 hours, and up to 28 days was referred to as having the early-onset and late-onset forms of neonatal bacterial meningitis, respectively. Table IA further highlights that in general, late-onset disease was relatively more common in the term, 20/28(71.4%) as against the preterm infant; 58.5%. However, this difference was not statistically significant and could have been so skewed by the inclusion of 12 cases of meningomyelocele.

The median age at presentation of neonatal bacterial meningitis was 9 days (range, 0 - 27).

The mean birth weight of the babies was 2,377g (range, 850 - 3,950) and the mean gestational age was 35.5 weeks (range, 26 - 42). Analysis of the overall live deliveries revealed that there were 3,496 and 1,249 term and preterm babies, respectively. The male: female ratio was 1.7:1. Of the inborn babies with the disease, 21 were preterm while 10 were term, with incidence of 16/1000 and 3.2 per 1000 detected for both groups, respectively; $p=0.001$. Corresponding figures for out-born babies were 20 and 18, respectively. Table IA also shows that preterm was more predisposed to having bacterial meningitis, 41 *versus* 28; $p=0.01$.

The total number of low birth weight (LBW) (<2,500g) infants delivered during study period was 1,026, compared with 3,247 and 472 of normal birth weight (≥2500g) and very low birth weight (VLBW), respectively. Fourteen, nine and 8 of these deliveries developed bacterial meningitis, respectively (Table IB). The incidence of bacterial meningitis was highest among the VLBW group of newborns; being 17 per 1000 live births, while it was 2.8/1000 for normal birth weight; $X^2=24.19$, $p=0.000001$. The incidence of meningitis for the LBW was 13.7/1000 live births. However, the difference between that of the VLBW and LBW was not statistically significant. Table IB further elucidates the specific rates in relationship to birth weight and gestational age.

The other identified predisposing risk factors were premature rupture of fetal membranes that later became prolonged, i.e. > 24 hours of drainage (n=20), presumed maternal bacteremia (chorioamnionitis or maternal peripartum pyrexia) (n=15), congenital anomalies, particularly of the nervous system (n=12), antepartum hemorrhage (placenta previa) (n=7), and home delivery (n=6).

Presenting Clinical Features

The symptoms and signs at presentation were mostly protean, vague and non-specific. Commonly mentioned problems were poor-feeding (n=47), excessive crying and restlessness (n=42), fever; core temperature =38.5oC (n=41), fast breathing (n=38),

vomiting (n=36) and seizures (n=31). All these symptoms were also documented objectively, while other signs comprised lethargy ((n=60), bradycardia (n=25), bradypnea (slow respiratory rate) (n=16), hypothermia; temperature <35.5^{0}C (n=15) and petechial hemorrhages (n=5). The main 'specific' neurological signs encountered were stupor with or without irritability (n=33), seizures (n=31), tense/bulging anterior fontanelle (n=23), high-pitched cry (n=14) and opisthotonus (n=6). The seizure types were generalized tonic in 14, multi-clonic; 10, and focal clonic; 5. The seizures were all preceded and/or associated with subtle features.

Bacteriology of Neonatal Meningitis

Of the 50 babies with 'definite' neonatal bacterial meningitis, 39 (78%) also had simultaneously positive blood cultures (Table IIA). These blood pathogens were 16 Gram-positive and 23 Gram-negative bacteria as was also cultured in the CSF. Table IIA also shows the relationship between the blood pathogens identified in neonatal bacterial meningitis and those seen in the CSF; as 78% of these neonates with 'definite' neonatal bacterial meningitis (n=50) and 'probable' neonatal bacterial meningitis (n=5) also had the same pathogens cultured in both CSF and blood. Furthermore, of the total 'definite' neonatal bacterial meningitis, twenty-two neonates had early-onset disease whilst late-onset type occurred in 28. All the 22 neonates also had proven positive cultures from their simultaneously taken blood specimens as was identified in their CSF. The remaining 19 neonates had 'probable' neonatal bacterial meningitis, out of which eleven cases had sterile CSF on culture but with isolation of pathogens from simultaneously obtained blood cultures; 2 with S. pneumoniae, N. meningitidis, untyped, 1, and H. influenzae, untyped in one. These sterile CSFs had significant pleocytosis (= 200 WBC x 10^6 /L; 60% polymorphonuclear leucocytes), which was further confirmed when subjected to (latex agglutination) immunodiagnosis.

The remaining 8 (11.6%) of 'probable' neonatal bacterial meningitis did not have CSF sample for analysis within the first 48 hours because of a) severity of the illness in 5 neonates, b) extensive defects in lumbar area, and c) late performance of lumbar puncture(after 48 hours of stabilization and therapy) in one full-term infant. The latter baby's CSF was, however, traumatic but the WBC exceeded the normal haemic proportions (1:800) by 200 cells/mm^3 (55% polymorphonuclear (PMN) and 45% lymphocytes); and it was sterile on culture. They all had highly suggestive 2 or more 'specific' clinical signs of meningitis with positive blood cultures.

There was more Gram-negative CSF isolates (28) compared to the Gram-positive isolates (22). However, the commonest pathogen was *S. aureus*, a Gram-positive microbe that was isolated in 13 cases. The commonest Gram-negative organism was *Escherichia coli*, 11, and this was followed by *Klebsiella oxytoca*, 7. It was noteworthy that some unusual organisms, not commonly isolated in neonatal bacterial meningitis, were encountered: *N.meninigitidis* in two *H.influenzae*, type *b* in one and *H. influenzae* (untyped) in one case. They contributed 0.6 and 2.2 per 1000 live births and admissions, respectively, to the overall incidence and proportion rates detected in study.

Gram-negative bacteria were generally more involved in late-onset disease; 17 *versus* 11 but specifically, *S. aureus* were most commonly isolated in late-onset disease, followed by *E. coli*. However, they both had equal propensity for early-onset meningitis. *H.influenzae* was responsible for late-onset disease.

Gram-negative pathogens caused almost twice as much mortality as the Gram-positive organisms; 11 (20%) *versus* 6 (10.9%). The contribution of *S. aureus*; 9.1% was, however, the highest of all isolated microbes.

Cerebrospinal Fluid Analysis

The detected range of WBCs in CSF of 'definite' neonatal bacterial meningitis was 17 - 3,950 x 10^6/L, with a mean of 647 and these were mainly PMN of between 60% - 100% on differential analysis. The CSF WBC was minimally raised (25 30 x10^6/L) in eleven (22%) and moderate; > 30 -100 x 10^6/L in 15 (30%). However, values in the remaining 36% were more than 100 x 10^6/L, with only three having very high WBC > 2,500 x 10^6/L. In 6 cases of 'definite' neonatal bacterial meningitis, CSF WBC was < 25 (range, 17 23 x10^6/L).

We observed that out of the 19 cases of 'probable' neonatal bacterial meningitis, CSF WBC in eleven ranged from 200 to 4,760 x 10^6/L. Blood culture and CSF latex agglutination positively confirmed *N. meningitidis* and *H. influenzae* in 2 of these cases.

The 17 of twenty-two 'definite' neonatal bacterial meningitis with minimally raised CSF WBC had early-onset disease while the remaining 5 (22.7%) had levels of < 60 x 10^6/L; 2, and > 100 x 10^6/L in 3.

A review of antimicrobial sensitivity patterns to some antibiotics (Table IIB) revealed that the cephalosporins and gentamicin were more effective against the Gram-negative microbes with over 90% and 100% sensitivity against *E. coli* and *Klebsiella* spp, respectively. *H. influenzae* were less sensitive to gentamicin *in vivo* as against *in vitro* findings, but they displayed 100% sensitivity to the third-

generation cephalosporin (ceftazidime). However, cefuroxime and ceftriazone provided ≥ 92% sensitivity over the Gram-negative microbes. We accede to the limited sample size of *H. inflenzae, N. meningitidis, Citrobacter* spp and *P. aeruginosa*, as were the spectrum of other relevant disks available during the study. Sultamicillin; a sysnthetic penicillin which is made of a combination of 'ampicillin sulbactam', showed 97% sensitivity over the Gram-positive organisms. The sensitivity patterns of *S. epidermidis* and *S. faecalis* were very similar to that of *S. pneumoniae*. However, none of the *S. aureus* and *S. pneumoniae* tested proved resistant to ceftriaxone and cefuroxime.

Outcome

Cases fatality was in 17 (24.6%) while 31 infants recovered fully without disability. Amongst the survivors with poor outcome, evolving neurological disabilities were noted; yielding a morbidity rate of 9/69 (13.0%). Such disabilities comprised sensorineural deafness, 3; hydrocephalus, 2; subdural effusion, 2; hemiparesis, 1; and afebrile (recurrent) seizures, 1. One of the hydrocephalus had meningitis caused by *H. influenzae*, untyped, and an 'arrest' occurred at the age of 4 months whilst on medical management (acetazolamide and diuretics), and the second (*S.aureus* as the agent) required ventriculoperitoneal shunt insertion.

No specific pathogen showed predisposition to any particular disability, with *S. pneumoniae, E. coli* and *N. meningitidis* differentially implicated in audiologic deficits. The case with recurrent/afebrile seizures had the problem occurring from the age of 7 months. Seven of the cases of meningomyelocele were lost to follow-up. A higher mortality was evident in early-onset disease as against late-onset; 12/22 (54.5%) *versus* 5/28 (17.9%), $p<0.001$. Overall, LBW had more risk for case fatality compared to normal birth weight; 14/39 (35.9%) *versus* 3/18 (16.7%), $p<0.01$, and mortality was predominant in the preterm, 13. There was no increased risk for mortality detected for gender difference. On the other hand, neonates who had raised CSF WBC and protein were more predisposed to death. Other encountered risk factors that increased mortality included presence of very low CSF glucose, four neonates (23.5%) with fatal neonatal bacterial meningitis exhibited hypglycorrachia; and out-born nature, as these showed a 4-fold rise in mortality as against being in-born. This latter risk factor was related to late presentation to hospital and prior antibiotic use; 3/31 (9.7%) *versus* 14/38 (36.8%). Only 5/56 (8.9%) neonates required repeat LP to ascertain reason for slow recovery and/or lack of good response, and confirm CSF sterility or otherwise.

Dexamethasone as an Adjunctive Use

On further analysis of contribution of dexamethasone to outcome, its usage and effect was analyzed in two phases of the study; Phase-1 and Phase-2. A better overall outcome was revealed with its usage as highlighted in Table III. The adjunct of dexamethasone (n=7 and 21 in Phase-1 and Phase-2, respectively), was associated with less mortality and more survivors without disabilities. The difference was particularly significant in Phase-2, when the use of dexamethasone was more controlled and routinely used alternately in study subjects. Furthermore, we carried out intra-phase comparisons of outcome, and there was significantly less mortality, (p=0.0004) and better recovery; p=0.007 in Phase2 of study. It is pertinent that clinical care and other variables were fairly constant during the study period, except for the more constant usage of dexamethasone in the latter half of the study-period. No side-effects/complications occurred in any infant. 3 cases had persistent hearing disability whilst 1 had transient hearing loss without dexamethasone adjunct. It was notable that hearing reverted to normal by 5 months of age in the infant with the transient hearing loss.

Also noteworthy was the result on analysis of effect of steroids *vis-à-vis* the nature of the causative microbe and mortality. In Phase-1, there was more preponderant case fatality among Gram-negative microbes without the use of dexamethasone; n=5 (60%) as against its usage, n=4 (25%), p= 0.001. It is pertinent to note that a highly significant mortality was observed with out the use of dexamethasone in Phase-2, irrespective of nature of microbes. No deaths occurred amongst neonates who had Gram-positive agents (n=7) *versus* 60% in those in which the steroid adjunct was not offered, p=0.0001. A similar pattern was notable for the Gram-negative microbes, where 7.1 %(n=14) and 63.6 %(n=11) mortality occurred with and without the use of dexamethasone as treatment adjunct, respectively.

At regular follow-up, surviving infants had frequent assessments of developmental status. Results of assessment using Griffiths' Mental Development Scales[27] done at 24 months in 35 infants were compared in different groups. Comparisons were made between time of onset of infection, and the use, or not, of dexamethasone with both times of onset combined. Neurological outcome was poorest in infants with early onset disease (n=14) and the assessment scores/performance of infants who received dexamethasone adjunct (n=15) were higher, although the lack of use (n=18) did not produce any unfavorable developmental status, mean (SD) mental age; 103.8 (1.8) *versus* 102.1 (2.0).

Table IA: **Onset of Neonatal Bacterial Meningiti in Relation to Birth Weight and Gestational Age in all Cases.**

	Early-Onset	Late-Onset	Total
	[1](n = 25)	[2](n = 44)	69
Birth Weight, g			
<1,500	6(2)*	14(6)	20(8)[+o]
1,500 - <2,500	11(8)	9(6)	20(14)[+o]
?2,500	8(4)	21(4)	29(9)[+]
Gestational Age, wk.			
< 37	17(10)	24(11)	41(21)[#]
?37	8(2)	20(8)	28(10)[*]

[1] n = 14, Early-Onset; for Inborn babies
[2] n = 17, Late-Onset; for Inborn babies
* Inborn babies in parentheses.
+ Higher risk of meningitis in low birth weight, p = 0.000001; X^2 = 24.19.
[o] No significant difference, p = 0.51, X^2 = 0.42.
[#] Higher risk for preterm, p < 0.001.

Table IB: Incidence of Neonatal Bacterial Meningitis in Relation to Birth Weight and Gestational Age (n=31)

Group of Newborn	Total live delivery	n (%)	Incidence/100(
Birth weight, g			
<1,500	472	8(25.8)	17.0[*]
1,500 - < 2,500	1,026	14(45.2)	13.7[*]
?2,500	3,247	9(29.0)	2.8[*]
Gestational age, wk			
?25 - 30	377	3(9.6)	8.0[1]
>30 - 35	721	15(48.4)	20.8[1]
>35 - 40	3,001	11(35.5)	3.7[2]
> 40	646	2(6.5)	3.1[2]

* *versus* [+] was highly statistically significant, X^2=24.19, p = 0.000001
[1] *versus* [2] also statistically different, p = 0.0001

Table IIA: **CSF and Blood Pathogens of Newborn Bacterial Meningitis and Onset in Relation to Mortality (n = 55)** [+]

Pathogen - Onset -	In CSF	- In Blood -		Mortality
		Positive CSF Culture (n=50)	Sterile CSF Culture (n= 5)	
(n=22) Late (n=28)	n(%)			Early
Gram-positive pathogen	22	16	2	11
11	6(10.9)			
Staphylococcus aureus	13	10	-	5
8	5(9.1)			
Streptococcus pneumoniae	4	3	2	1
3	1(1.8)			
S. epidermidis (S. albus)	4	2	-	3
1	0			
Streptococcus faecalis	1	1	-	1
-	0			
Gram-negative pathogen	28	23	2	11
17	11(20)			
Escherichia coli	11	10	-	5
6	4(7.3)			
Klebsiella oxytoca	7	5	-	2
5	3(5.5)			
Coliform spp.	3	3	-	2
1	2(3.6)			
Neisseria meningitidis	2	1	1	1
1	1(1.8)			
Citrobacter spp.	2	1	-	-
2	0			
H. influenzae, type b	1	1	-	-
1	1(1.8)			
H. influenzae, untyped	1	1	1	-
1	0			
Pseudomonas aeruginosa	1	1	-	1
0	0			

+ n = 50 in 'definite' neonatal bacterial meningitis.
n = 5 in “sterile” CSF culture, i.e. 'probable' neonatal bacterial meningitis.

Table IIB: **Antibiogram of Some CSF Bacterial Isolates**

	Total Isolates Tested, n (% Sensitivity)								
Antibiotic	**Sa**	**Sp**	**Ec**	**Ko**	**Co**	**Cit**	**Nm**	**Hi**	**Pa**
Ampicillin	11(40.5)	4(98.7)	11(40.6)	7(30.5)	3(18)	2(0)	2(100)	2(50)	1(25)
Carbenicillin	10(95.5)	NT	9(88.7)	6(91.5)	2(5)	NT	NT	NT	1(100)
Ceftazidime	13(94)	4(88.5)	11(96)	7(93)	3(85)	2(100)	2(100)	2(100)	1(50)
Cefriazone	13(100)	4(100)	11(92)	7(92.5)	3(92)	2(100)	2(100)	2(100)	1(100)
Cefuroxime	13(100)	4(100)	11(92)	7(92.9)	3(92)	2(100)	2(100)	2(100)	1(50)
Chloramphen	5(39.5)	4(28.5)	11(91)	7(92.5)	3(100)	2(50)	2(50)	2(50)	1(0)
Cloxacillin	12(42)	4(63)	9(22.5)	6(25)	3(18)	2(0)	2(100)	2(50)	1(0)
Gentamicin	12(96)	3(65)	11(100)	7(100)	3(100)	2(50)	2(100)	NT	1(100)
Ofloxacin	13(100)	4(100)	11(100)	7(100)	3(100)	2(100)	2(100)	NT	1(100)
*Sultamicillin	13(96.5)	4(100)	11(84)	7(88)	3(69)	2(50)	2(100)	2(100)	1(50)

*a *beta-lactamase* stable ampicillin sulbactam combination, with the trade-name Unasyn®

Abbreviations: CSF = Cerebrospinal fluid Sp = *Streptococcus pneumoniae* Ec = *Escherichia coli*
Ko = *Klebsiella oxytoca* Co = *Coliform* spp. Cit = *Citrobacter* spp
Nm = *Neisseria meningitides* Hi = *Haemophylus influenzae* Pa = *Pseudomonas aeruginosa*
Chloramphen = Chloramphenicol NT = Not tested

Table III: **Use of Steroids (Dexamethasone) and the Quality of Recovery from Neonatal Bacterial Meningitis**

Phase of study	Mortality, n (%)	[s]Recovery with disability, n (%)	Full Recovery, n (%)
[#]**Phase-1**			
Dexamethasone use, n = 7	*2 (28.6)	2 (28.6)	+3 (42.9)
No Dexamethasone use, n = 11	*4 (36.4)	1 (9.1)	+6 (54.6)
[#]**Phase-2**			
Dexamethasone use, n = 21	**1 (4.8)	4 (19)	++16 (76.2)
No Dexamethasone use, n = 18	**10 (55.6)	2 (11.1)	++6 (33.3)

[s] Disabilities/handicaps included; Hearing deficit (permanent), 3; Subdural effusion, 2; Hydrocephalus, 2; Hemiparesis, 1; and Afebrile/Recurrent Seizure, 1.
[#] Significantly less mortality in shown in Phase 2, $X^2 = 12.2$, $p = 0.006$.
* Yates' corrected $X^2 = 0.04$, $p = 0.84$
* Yates' corrected $X^2 = 0.09$, $p = 0.76$
** $X^2 = 12.3$, $p = 0.0004$.

DISCUSSION

The incidence of 6.5/1000 live births of neonatal bacterial meningitis confirmed an increasing trend in Nigeria when other areas are maintaining a relatively stable level, for instance, rates of 0.32/1000 in the Netherlands,[12] 0.25-0.32 per 1000 in England,[2,4,21] 0.99/1000; North America[31] and 0.69 1.9/1000 in other regions of Africa.[3, 8, 9] Further glaring is our exceedingly high rate which surpassed a previous rate of 1.9 per 1000 in another area of this country,[3] though in agreement with the noted evidence of increasing trend of bacterial meningitis.[10] We must admit that our referral hospital, which also serves three other contiguous countries, may have had a bias for more admissions of high-risk pregnancies that reside great distances away to a tertiary hospital. Such a scenario would be different from another hospital that receives a larger proportion of lower-risk pregnancies from nearby locations. However, it remains pertinent that the rate of infection and its surveillance method, *vis-à-vis* poor hygienic condition, requires more vigorous assessment and good control of infections in the developing world.[3, 19, 20]

Similarly intriguing was the was finding of a 6-fold increase in the incidence of neonatal bacterial meningitis amongst the LBW infants, and this is consistent with previous studies.[2-4, 32] Our study also confirmed that the preterm was more significantly exposed to the risk of bacterial meningitis overall; $p < 0.0001$.These gestational-, and birth weight-related patterns of increased risk result from the complex interactions of several host defense deficiencies and

microbial characteristics. The younger and smaller neonate is particularly vulnerable to bacterial disease because of the well known inadequate maturation of cell and antibody mediated immune mechanisms, coupled with other physical factors. Wenger et al,[13] de Louvois *et al* [2] and Hristeva *et al* [4] had earlier shown similar trend for the preterm.

The etiologic spectrum of neonatal bacterial meningitis in our unit was noteworthy: there was the emergence of unusual pathogens. The commonest single pathogen overall was a Gram-positive organism, *S. aureus*. No GBS and *L. monocytogenes* were isolated despite their common frequency in other regions.[2, 4, 9-13, 21] The lack of GBS further confirms the observations by others that this pathogen is an uncommon cause of disease in Nigeria.[3, 8, 19, 20] The reasons for such a rarity are not clear but it could speculated to be related to the methods employed in maintaining genital hygiene, such as douching, or some other unexplained familial/genetic inhibitory capacity against the GBS pathogen. However, our encounter of neonatal bacterial meningitis caused by *N. meningitidis* was intriguing since such pattern was rare, in spite of the hospital being within the African "meningitis belt".[18]

Only one case of neonatal bacterial meningitis caused by *N. meningitidis* and none causal to *H. influenzae* was encountered over a 10-year period by Fortnum and Davis.[21] Although Wenger *et al* [13] found no *N. meningitidis* but a few *H. influenzae* meningitis over a similar period, their opinion being that neonatal disease is more likely to be caused by non-type *b* strains, was not supported by our finding. The *H. influenzae*, type *b* in our study was invasive and it had also been isolated from simultaneous blood culture specimen. The rarity of these isolates causing meningitis has been attributed to the acquisition of maternal antibodies directed against capsular antigens, [33, 34] and to a lesser extent by the immunological effect of breast-feeding.[35] It is possible that the observed emerging trend in our study, therefore, may be related to a rapidly waning maternal humoral immunity.

In view of the associated high mortality and neurological sequelae, an early diagnosis requires diligence and high priority. However, because clinical assessment cannot distinguish septicemic infants with coexisting meningitis from those without meningitis, it is vital to do blood culture alongside the lumbar puncture for CSF evaluation. The documentation of 15% neonatal bacterial meningitis being associated with concomitant negative blood culture[36] and 85.7% positive blood culture (over a 7-year period)[4] is in consonance with the 78% positive culture rate seen in the present study. Therefore, with such an increased probability of simultaneous isolation of pathogens via blood culture (particularly of early-onset), it is mandatory that a blood culture must be done whilst doing a lumbar puncture.

Hendricks-Munoz and Shapiro[37] have shown that meningitis in the first six hours of life is unusual, and that the value of CSF examination is minimal in this age-group (<48 hours of age). The pattern of CSF disturbance in our neonatal bacterial meningitis was revealing. Though a diagnosis of bacterial meningitis cannot be excluded by a normal CSF chemistry or a normal CSF WBC, [37-39] a minimally raised WBC (25-30x10^6/1) was seen in 22% of the 'definite' cases in this study while 6 (12%) had levels further lower. A low CSF WBC in the presence of infection may be due to possible interplay of previous antibiotic exposure and/or poor mounting of inflammatory response, or some other genetic/regional difference. The latex agglutination test was not used routinely in all our cases but was only employed as a valuable supportive tool to the routine bacteriological examination of CSF, as opined by Varaine *et al* [26]

The overall mortality was 24.6%, with the Gram-negative pathogens being about two-fold more than the Gram-positive. Although not a randomized evaluation, however, the routine usage dexamethasone as an adjunct along or before the first antibiotic was significantly associated with less mortality, $p < 0.0004$, $\div^2 = 12.3$ (Table III). There was no permanent hearing deficit identified amongst the survivors with disabilities who had adjunctive dexamethasone, while three had sensorineural deafness without it. The pathogenesis of the hearing disabilities was thought to be acquired via the meningitic process i.e. the inflammatory involvement of the cochlea and labyrinth structures.[40 - 42] Furthermore, our strict consideration of the adverse risk criteria for the occurrence of congenital auditory deficits,[29,30] assisted the verification of acquired sensorineural hearing loss. It is possible that more mild hearing loss may have been detected by BAER, had it been used in this study.

This improved outcome with adjunctive dexamethasone corroborates the suggestions of other workers.[2, 14, 16, 43-45] Most of these studies have not been done on neonates, but an older infants and children. However, studies from developing countries had not shown such benefits [46] and none of these clinical studies or assessments was also focused on neonates. This is in spite of the longstanding evidence that much of the cerebral damage is the direct consequence of the activation of host inflammatory pathways rather than a direct effect of the invading organism.[5, 47, 48] It must be said that some clinicians are wary of using dexamethasone because it may mask the presentation of underlying infections, and hence do not routinely use it as a adjunct.[49]

Although we accede that our dexamethasone offer in the second-half of study period was unselective, however, the treatment offered covered the same trend of disease profile, especially in the in-born infants. Furthermore, we must acquiesce that our dexamethasone data are not the result of a randomized evaluation.

The efficacy of mannitol in the management of cerebral edema/raised ICP remains controversial and debatable. Levene *et al* [50] have found it only useful in raised ICP from perinatal asphyxial insult.

The best antimicrobials included gentamicin and ceftazidime until the sensitivity differential is ascertained. Cloxacillin had to be dropped from empiric use in view of report of its ineffectiveness and as was noted during study. It is pertinent that our empiric antibiotic use was at variance with the developed/affluent countries where the cephalosphorins are of standard usage. However, their costs are excessive in our nations' setting. Sultamicillin (synthetic penicillin) would be an effective alternative in the parenteral form, as appropriate cover was provided against both Gram-positive and Gram-negative organisms, and its efficacy has previously been documented.[51] Finally, with such high rate of CSF cultures that grew mostly Gram-positive organisms, vancomycin (though not tested against) could be a good initial empiric treatment.

In conclusion, our research has revealed a changing trend of neonatal bacterial meningitis with emerging new pathogens in Nigeria, and better outcome with adjunctive dexamethasone. It is pertinent that all survivors should be referred for full neuromotor and audiological assessments for early detection of sequelae, learning or developmental disabilities, or communication disorders. All feasible efforts should be proffered for infection control, continuing epidemiology and further expert surveillance. Furthermore, larger studies to delineate the significant CSF WBC cut-off level that correlates with 'definite' neonatal bacterial meningitis and the effect of steroidal adjunct are warranted.

ACKNOWLEDGEMENTS

We would like to thank the Resident Doctors and Nursing Personnel of the Special Care Baby Unit for their good care, Mallam Abdulmumuni, Laboratory Assistant; for his assistance, and all parents and their babies for their considerable cooperation.

Gratitude goes to Mr. Adelaja M. Adetunji of M.I.S. Unit, Usmanu Danfodiyo University Teaching Hospital, and Sokoto for preparation of manuscript.

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