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BACTERIAL AETIOLOGY, ASSOCIATED FACTORS AND IMMEDIATE OUTCOME OF NEONATAL MENINGITIS AT THE UNIVERSITY TEACHING HOSPITAL, LUSAKA

BY

Fubisha Captain Robert, B. SC. H.B., M. B. Ch. B.

A dissertation submitted to the University of Zambia in partial fulfilment of the requirements for the degree of Masters in Paediatrics and Child Health

DEDICATION

I dedicate this dissertation to my wife, Hellen and my daughter Michèlle.

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APPROVAL

The University of Zambia approves this dissertation of Fubisha Captain Robert in partial fulfillment of the requirements for the award of the Master of Medicine degree in Peadiatrics and Child Health.

Examiner 1.

Signature.....Date....14.02.05

Examiner 2.

Signature....MNkoma.....Date....02.02.05....

Examiner 3.

Signature....MNkoma.....Date....02.02.05.

for Ext Examiner

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LIST OF ABBREVIATIONS

CSF: Cerebral spinal fluid

CNS: Central nervous system

CNS1: *Coagulase negative staphylococcus*

E. coli: Escherichia coli

GBS: Group B streptococcus pneumonia

K. pneumonia, Klebsiella: Klebsiella pneumonia

S. pneumonia: Streptococcus pneumonia

NICU: Neonatal Intensive Care Unit

SVD: Spontaneous vaginal delivery

C/S: Ceasarian section

LP: Lumbar puncture

PROM: Premature rupture of membranes

USA, US: United States of America

UTH: University Teaching Hospital

Spp.: Species

MOD: Mode of delivery

Bwt: Birthweight

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ABSTRACT

Introduction: Neonatal meningitis is a devastating disease, and its mortality and morbidity is high. At the University Teaching Hospital (UTH) in Lusaka, however, no study has looked specifically at the disease, and controversy exist on whether neonates admitted to the General Paediatric Wards should be treated with the same drugs as those on the Neonatal Intensive Care Unit (NICU), or whether born at home or at the institution. Studies, however, have been done in older children. It is of paramount importance to document neonatal sepsis on any neonatal unit from time to time, as the causative organisms differ not only from place to place, but also from time to time on the same unit. Owing to resource constraints, this is not done at UTH.

Aims: The study was undertaken to determine the magnitude of neonatal bacterial meningitis, its aetiology and sensitivity patterns, associated factors and immediate outcome in neonates admitted to the General Paediatric Wards and the Neonatal Intensive Care Unit of the University Teaching Hospital, Lusaka. It was also to suggest a possible treatment regimen.

Methodology: This was a descriptive prospective study of neonates with a clinical diagnosis of neonatal sepsis admitted to UTH in the General Paediatric Wards (Group 1) and the NICU (Group 2) from 1stMarch 2002 to 28th February 2003. Group 1 has about 22 000 admissions per year while Group 2 about 3 000 per year. The neonates were recruited to the study by consecutive sampling.

Results: The clinical features and microbiology findings of the twenty-two neonates with meningitis are presented. Eight of these neonates are from Group 1 and 14 from Group 2. The prevalence in Group 1 was 5.6% and that in Group 2 was 4.6%, overall prevalence being 5%. *Klebsiella pneumonia* (32%) and *streptococcus pneumonia* (22.7%) were the commonest organisms isolated. Some isolates of *K. pneumonia* showed resistance to ampicillin chlomphenicol and cefotaxime, whilst one isolate was sensitive to gentamicin. *Streptococcus pneumonia* was 100% sensitive to chloramphenicol and 80% sensitive to benzyl penicillin but 25% of the isolates were resistant to cefotaxime. All isolates were fully sensitive to ciprofloxacin. The mean age at diagnosis of neonates in Group 1 was 11.1 days and 3.8 days in Group 2. This was statistically different, $p = 0.0142357$. There was no statistical difference in the 2 groups with regard to clinical features and the microbiology findings.

Conclusion: In this study, the prevalence of neonatal meningitis in neonates admitted with clinical sepsis to UTH was found to be 0.05. The most prevalent organism isolated was *K. pneumonia* followed by *S. pneumonia* and some isolates were resistant to cefotaxime. According to the culture sensitivities in this study, empirical treatment with ciprofloxacin is the appropriate first line of treatment in all neonates with suspected meningitis or sepsis.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background 1nformation

Neonatal meningitis refers to meningitis in the first twenty-eight days of life. This is a serious infection involving the subarachnoid space with associated high morbidity and mortality. Any ill neonate is considered to have septicaemia and/or meningitis until proven otherwise by a sepsis screen, which includes a lumbar puncture. Progression of a septicaemia to meningitis is rapid in this age group and its effects on the growing brain are profound [1,2,3,16].

1.2 Statement of the problem

In spite of the improvements in neonatal intensive care, neonatal meningitis is still a serious disease, with high mortality and morbidity. Those neonates surviving the disease are at high risk of long-term sequelae [1,2,3,7].

At UTH, no study has been done specifically on neonatal meningitis so as to determine the extent of the problem. Studies have however been done in older children.

One study looked at age groups 0-12 months, 12-24 months and over 24 months respectively. The commonest organism isolated was *pneumococcus* followed by *H. influenza* [28]. The same authors also reported on three cases of salmonella meningitis in infancy. This was on a 13-day-old male neonate, 3-week-old female neonate and a 9-month-old female infant who all died, despite using appropriate antibiotics in optimal doses [58].

Another study dealt with neonatal septicaemia on NICU. In this study, 32.6% of the babies had positive blood cultures. *Coagulase negative staphylococcus* constituted 36.7%, while both *Klebsiella* and *Staphylococcus aureus* constituted 23.3% each [48]. It is of paramount importance from time to time, to document neonatal sepsis on any neonatal unit, as the causative organisms differ not only from place to place, but also from time to time on the same unit [9]. This, however, is not done at UTH due to resource constraints.

1.3 Study justification

No studies so far have been done to specifically look at and assess neonatal meningitis at UTH, Lusaka. Knowing the prevalent bacterial causes of the disease and changing patterns of sensitivities, will result in development of appropriate protocols. This study thus looked at the organisms isolated, their sensitivity patterns as well as the obstetric and neonatal factors. It also looked at the clinical features in the babies with meningitis.

CHAPTER TWO

2.0 LITERATURE REVIEW

Neonatal meningitis is a serious infection of the central nervous system with a high rate of complications, chronic morbidity and high mortality. The disease differs from that in older children with regard to incidence, aetiology and the clinical picture [1,2,3].

2.1 Prevalence

Some studies have shown that there is some drop in the incidence of the disease in developed countries [7,41]. Other studies have actually contradicted this. The incidence in developed nations is around 0.25 to 0.5 per one thousand live births [31,33,43].

In the developing countries, the incidence is higher, at 0.5 to 2 per thousand live births [44, 45].

20% of the late onset sepsis cases and 10% of the early onset sepsis case are complicated by the disease [9,46]. The more premature the neonate is, the higher the risk of developing the disease [9,31].

2.2 Aetiology

The causative bacterial agents are varied. These include *Group B streptococcus, E. coli, L. monocytogenes, K. pneumonia, S. pneumonia,* other *Streptococci, H. Influenza, staphylococci* and rarely organisms like *salmonella.* However, *Group B streptococcus* and gram negative bacteria play an important role [1,2,6,7,9,11,28,44,58,70,71,78,79].

In the United Kingdom (UK) and the United States (US), *Group B streptococcus, E. coli* and *L. monocytogenes* are the major pathogens isolated [2,29]. In the developing countries, the commonest isolated pathogens are *E. coli* and *K. pneumonia* [6,11,44,57].

H. influenza, Streptococcus pneumonia and *Neisseria meningitides* common in the older children are only found in the late neonatal period or in the second month of life [32, 33].

2.3 Predisposing factors

Foetal, perinatal and neonatal factors play an important role in the evolution of the disease [1, 2,3,9,16,48].

Vaginal flora, maternal illness, age, parity, premature rupture of membranes and chorio-amnionitis are the maternal factors that play a vital role. Foetal risk factors include gestational age, sex, birth asphyxia, respiratory distress syndrome (RDS), meconium aspiration and congenital anomalies. Premature delivery, low birth weight (LBW), asphyxia, assisted ventilation, catheterisation and any surgical intervention are important neonatal factors [1,2,16,48,61,80].

Neonatal immunity though well developed is immature functionally. Both specific and non specific are affected. Abnormal chemotaxis, phagocytosis and bactericidal activity exist in the defective granulocytic function. Opsonization is also abnormal due to low complement levels. As regards antibodies, only IgG are high enough in the neonate at birth as it is actively transported across the placenta in utero. Only traces of IgA, IgE and IgM are found at birth - their significant production starts at birth [1,16,50].

2.4 Pathophysiology of meningitis

The brain and spinal cord are relatively well protected, and infections of the central nervous system are uncommon. However, once microorganisms have gained access to the central nervous system, the infection spreads rapidly by way of the CSF pathway [21]. The severity of the clinical illness depends on the virulence of the infective agent and susceptibility of the host. Young infants are more likely to develop meningitis, as the presence of neutralising antibodies to bacterial antigens in the vascular space is age related. Owing to their immature immune system, organisms such as candida can also cause serious and fatal infection of the nervous system [5,9,21,69,75].

Meningitis may involve the durapachymeningitis - or the pia and the arachnoid - leptomeningitis. The latter is by far, the commoner, the term meningitis is often used instead of leptomeningitis [21].

Acute pyogenic meningitis

This is caused by infection of the subarachnoid space. The pia-arachnoid membrane becomes inflamed and exudate is added to the CSF [12,16,21].

Routes of infection

Meningitis occurs as a result of septicaemia. Port of bacterial entry into the intravascular space in neonates includes the gastrointestinal and respiratory tracts, the umbilical stump and any area on the skin with break in the epithelium, e.g., due to birth trauma. The disease can occur as a complication of catheterisations, lumbar puncture or any invasive surgical procedure [1,2,12,13]. Central nervous system malformations are important, e.g., dermal sinuses, myelomeningocoeles by which bacteria get direct access to the central nervous system [1,2,12,16,21].

Bacterial penetration across the blood-brain barrier

Bacteria are able to penetrate the blood brain barrier (BBB) and invade the central nervous system through para cellular and/or transcellular mechanisms. For *E. coli* K1 for example, transcellular penetration, which is through transcytosis across the BBB, has been demonstrated. The same mechanism has been demonstrated to exist *for Group B streptococcus, Listeria monocytogenes, Citrobacter freundii* and *Streptococcus pneumonia strains.*

E. coli K1 genes comp A ibe A, ibe B and yij are the genes involved in the invasion of the micro-vascular endothelium of the brain [5].

Potent pro-inflammatory cytokines, notably tumour necrosis factor-alpha (TNF-alpha) and interleukin-1 (IL-1) [34,36,37] produced by stimulation of macrophage-equivalent brain cells (like astrocytes, microglia) by bacterial products released within the subarachnoid space, liberate a number of inflammatory substances (e.g., IL-6, IL-8, phospholipase A, platelet activating factor, arachidonic acid metabolites, granulocyte-macrophage colony-stimulating factor, macrophage derived proteins) [14,35] which play a vital role in promoting alterations of brain endothelium that lead to disruption of the BBB.

Structural changes

Once large numbers of neutrophils enter the subarachnoid space, the locally produced cytokines are stimulated to degranulate and release oxygen radicals and other proteolytic substances. These products induce cytotoxic changes in cerebral tissue and, with plasma components, which include proteins, make the CSF more viscous, and interfere with reabsorption of the fluid at the villi [14, 35]. These events lead to cerebral oedema, increased

intracranial pressure, loss of cerebral auto-regulation, diminished cerebral blood flow and ultimately an irreversible focal or widespread brain damage may occur [14,35,23,38].

CSF is usually turbid. Microscopy reveals numerous neutrophils. Protein content is raised and sugar reduced or absent. The causative organisms are often apparent on Gram stain, although in some cases, they can only be detected by culture [11,12,21,25,26,27,29].

Vigorous early and appropriate treatment results in resolution of the infection with little or no residual damage. Late or inadequate treatment may allow progression of the disease to development of complications. The meninges become thickened and oedematous and organisation of fibrin deposits leads to obliteration of the foramina of ventricles and/or some degree of obstruction. Cranial nerves may be involved with resulting palsies. Similar changes can occur in the spinal meninges with involvement of nerve roots [12, 16,21,23,39,40].

2.5 Clinical features

Features of neonatal meningitis are non-specific. Therefore, any neonate who is ill must be considered to have septicaemia and/or meningitis until proven otherwise. Some of the features include lethargy, poor feeding, vomiting, fever, irritability and convulsions. Bulging anterior fontanel is a useful but a late feature [1,2,51,73,82].

2.6 Treatment

Prompt appropriate and adequate treatment is of paramount importance, and includes not only antibacterial but also a steroid like dexamethasone. The latter helps a great deal in reducing the inflammatory process and consequently results in quick recovery and less residual effects [12,14,16,23,34,36]. In a clinical trial done in Irbid [72], however, dexamethasone

added to antibacterials in neonatal meningitis did not alter the outcome. Cefotaxime is the drug of choice and is used the world over [6,7,44,60].

2.7 Complications and prognosis

The complications of the disease can be divided into immediate and long term. The former include seizures, increased intracranial pressure, hydrocephalus, nerve palsies, stroke, cerebellar or cerebral herniation, transverse myelitis, ataxia, thrombosis of the venous sinuses, subdural effusions and cerebral abscesses. Syndrome of inappropriate anti-diuretic hormone secretion, pericarditis, arthritis, thrombocytosis, esinophilia, may also occur during treatment. Long-term sequelae include seizures, hydrocephalus, cerebral palsy, blindness, deafness, mental retardation and behavioural problems [1, 2,12,16,23,24,59,68,77].

Most of the studies show that 30 to 50% of the survivors have adverse neurological complications [12,17]. Prognosis is worse in preterm babies [9,11,12,79]. In general, neonates with *Group B streptococcus* do better than those with Gram-negative bacteria. Up to 70% of neonates surviving the disease due to the former have been found to be normal [12, 18]. It has also been found that the higher the CSF protein levels, the worse the prognosis [11, 28].

E. coli is associated with a mortality of about 40% and more than 50% of the neonates surviving the disease have neurological sequelae [81].

2.8 Prevention

Measures are now being taken in the prevention of the disease.

With regard to *Group B streptococcus*, ampicillin or penicillin is recommended intra-partum to women who are at risk. It is also given to women whose rectal or vaginal swabs

are positive for the organism at term. Ampicillin is also given to neonates with unknown results [52, 65,67.]

Better outcomes are observed in women with premature rupture of membranes and are given antibacterials compared to those who have none [53.]

Intravenous immune-globulins have shown a lot of benefit in prevention of sepsis [54,55.]

In some regions, white blood cells have been used so as to alter the outcome [56.]

Apart from the cultures of both rectal and vaginal swabs, immunological tests for rapid detection of heavily infected parturients are now available [62]. Lavage of the birth canal with chlorhexidine has been found to be very useful [63.]

Research to develop vaccine for *Group B streptococcus* is still ongoing and could theoretically be based for Alberta neonates, for example on the serotypes Ia, III and V [in] a conjugate vaccine or serotypes II and V conjugated with the protein C in a GBS vaccine [64]. As regards *E. coli*, the commonality shown between 018:K1:H7 isolates from women with acute cystitis and neonates with bacterial meningitis may just be the way to new approaches to prevention [66.]

CHAPTER THREE

3.0 STUDY OBJECTIVES

3.1 General Objective

To determine bacterial aetiology, associated factors and immediate complications of neonatal meningitis at the University Teaching Hospital, Lusaka.

3.2 Specific objectives

i. To determine the prevalence of neonatal meningitis at UTH.

ii. To establish the bacterial causes of neonatal meningitis and their sensitivity patterns.

iii. To study the common associated factors in the disease.

iv. To study the immediate outcome of the disease.

v. To recommend a treatment regimen of neonatal meningitis.

CHAPTER FOUR

4.0 METHODOLOGY

4.1 Study setting

This study was conducted on the Neonatal Intensive Care Unit (NICU) and General Paediatric Ward Nurseries at the University Teaching Hospital (UTH), Lusaka. The NICU has a bed capacity of 107, consisting of 43 incubators and 64 cots. Approximately 3000 babies are admitted to the unit per year, with a few above 28 days of age.

The General Paediatric Wards have a total bed capacity of 368, with 242 cots. There are about 22000 admissions to General Paediatric Wards per year with approximately 25% being babies less than 6 months old [4,8].

4.2 Study design

This was a descriptive prospective study of neonates admitted to UTH with a clinical diagnosis of septicaemia and/or meningitis from 1st March 2002 to 28th February 2003.

4.3 Study population

This consisted of all neonates admitted to NICU and General Paediatric Ward Nurseries with a provisional diagnosis of septicaemia and/or meningitis during the study period.

4.4 Selection of subjects

Inclusion criteria:

i. Babies 0 to 28 days old admitted with the provisional diagnosis of septicaemia and/or meningitis.

ii. Must have a CSF gram stain or culture positive for meningitis

Exclusion criteria:

i. Babies more than 28 days old

ii. Negative CSF for meningitis

4.5 Definition of neonatal meningitis

In this study, provisional diagnosis of neonatal meningitis was made in an ill baby who has at least one of the signs of infection, like, lethargy, poor feeding, unstable temperature, e. t. c.

Confirmed meningitis: This will refer to a positive CSF culture.

Unconfirmed meningitis: This will refer to a neonate whose CSF culture will have no growth but has white blood cells more than $30mm^3$.

4.6 Sampling

All babies 0 to 28 days old admitted to NICU and General Paediatric Wards within the study period with the clinical diagnosis of septicaemia and/or meningitis meeting the inclusion criteria were recruited to the study (consecutive sampling).

4.7 Sample size

The sample size was determined by the number of neonates admitted to UTH within the study period and meets the criteria for recruitment.

4.8 Subject management

Information was collected using a standardised questionnaire, which included maternal and neonatal factors. See appendix (page 43).

4.9 Follow-up of study subjects

All babies were followed up till discharge or death.

4.10 Collection of CSF

After evaluation of the neonate, under aseptic conditions LP was done and CSF collected into a sterile plain bottle with no additives.

4.11 Bacteriology

A record of macroscopic appearance of the CSF collected was made and sent to the laboratory in the shortest possible time.

In the laboratory, CSF was visualized for colour, turbidity, and presence of deposits or otherwise. The CSF cell-count was determined using a pipette and counting chamber; differential white cell-count was also determined. Gram-stain smear of the CSF was prepared and examined for bacteria, and a provisional diagnosis made from their morphology. The CSF was then streaked on chocolate agar, blood agar and McConkey agar and incubated over-night in 10% Co_2 at 37^0C. The colonies growing were checked after 24 and 48 hours of incubation, and identified by their morphology and biochemical tests. Sensitivity patterns were also established.

4.12 Treatment protocol

Treatment was initiated by the attending medical practitioner who decided which drugs to use. Empirical combinations of benzyl penicillin with gentamicin, ampicillin with cloxacillin and ampicillin with chloramphenicol were used. Drugs were changed later, depending on the culture result or the clinical response.

4.13 Logistics, budget and funding

The study was done as part of the Hib-Paediatric Bacterial meningitis (H1b-PBM) Surveillance Network sponsored by WHO/AFRO, currently being undertaken in the Department of Paediatrics and Child Health. The Network provided almost all the tools for investigations.

The costs below were borne by the principal investigator:

Stationary K150 000.00

Secretarial services K70 000.00

Biostatistician K250 000.00

Total K470 000.00

4.14 Data processing and analysis

The data collected was analysed by use of Epi info 6.

For analysis, the babies from the General Paediatric Wards were denoted as Group 1 and those from the NICU as Group 2.

4.15 Ethical consideration

Permission to conduct the study was granted by the University of Zambia (UNZA) Research and Ethical Committee as well as by the Department of Paediatrics and Child Health.

CHAPTER FIVE

5.0 RESULTS

During the study period, that is, from 1st March 2002 to 28th February 2003, a total number of 142 neonates from Group 1 and 302 neonates from Group 2 had CSF taken for the diagnosis of meningitis. A total number of 22 of these neonates were confirmed to have meningitis and were recruited to the study.

Table 1. Prevalence

Month	Group 1 N=8	Prevalence	Group 2 N=14	Prevalence	Total prevalence
March 2002	0	-	0	-	-
April 2002	0	-	0	-	-
May 2002	0	-	1	0.003	0.002
June 2002	0	-	2	0.007	0.004
July 2002	1	0.007	0	-	0.002
August 2002	1	0.007	1	0.003	0.004
September 2002	2	0,014	2	0.007	0.009
October 2002	2	0.014	3	0.010	0.011
November 2002	1	0.007	1	0.003	0.004
December 2002	0	-	1	0.003	0.002
January 2003	1	0.007	2	0.007	0.007
February 2003	0	-	1	0.003	0.002
Overall	8	0.056	14	0.046	0.050

The prevalence for Group 1 was 0.056 and 0.046 for Group 2, the overall prevalence being 0.05.

14 of the 22 (64%) neonates were male and 8 (36%) were female Table 2 shows the characteristics of the babies.

Table 2. Characteristics of babies with meningitis

Characteristic	Group 1 N=8	Group2 N=14	*P* value
Average weight (kg)	2.5	3	0.22754655
Average age at diagnosis (days)	11.125	3.857	0.01423578
Male sex	4	10	
Female sex	4	4	0.31485395

5.1 Isolated organisms

K. pneumonia (31.8%) was the commonest organism isolated followed *by Streptococcus pneumonia* (22.7%) and *Streptococcus* Spp. (9.1%). *Acinetobacter Spp., CNS1, Salmonella Spp. and Pseudomonas Spp.* were the least isolated each with 4.5%. Mixed growth constituted 18.2% (Table 3).

Table 3. Isolated organisms

Organism	Group 1 N=8	Group 2 N=14	Total
Acinetobacter	0	1 (7.1%)	1 (4.5%)
K. pneumonia	2 (25%)	5 (35.7%)	7 (31.8%)
Mixed growth	1 (12.5%)	3 (21.4%)	4 (18.2%)
CNS1	0	1 (7.1%)	1 (4.5%)
Pseudomanas Spp.	1 (12.5%)	0	1 (4.5%)
Salmonella Spp.	1 (12.5%)	0	1 (4.5%)
S. pneumonia	3 (37.5%)	2 (14.3%)	5 (22.7%)
Streptococcus Spp.	0	2 (14.3%)	2 (9.1%)
Total	8 (36.4%)	14 (63.6%)	22 (100%)

Chi-square: 7.81

Degrees of freedom: 8

P value: 0.45211586

5.2 Antibacterial susceptibility

All the organisms isolated were subjected to sensitivity tests with the exception of a mixed growth. However, the number of antibiotics tested against depended largely on the availability of the discs at a particular time. Tables 4 to 7 illustrate the sensitivity patterns done.

Table 4. Antibacterial sensitivity pattern of *Klebsiella pnuemonia*

Isolates N=7	Benzyl penicillin	Ampicillin	Gentamicin	Chloramph-enicol	Cefotaxime	Ciprofloxac-in
1	Not done	Not done	Not done	R	Not done	S
2	Not done	R	S	R	Not done	S
3	Not done	R	Not done	S	S	S
4	Not done	Not done	Not done	R	R	S
5	Not done	R	Not done	R	R	S
6*	Not done	R	Not done	S	S	S
7*	Not done	Not done	Not done	R	Not done	S

NB. R: Resistant

S: Sensitive

*: From Group 1

Table 5. Antibacterial sensitivity patterns of Streptococcus pneumonia

Isolates N=5	Benzyl penicillin	Ampicillin	Gentamicin	Chloramph-enicol	Cefotaxime	Ciprofloxac-in
1	PS	Not done	Not done	S	Not done	S
2	S	S	Not done	S	R	S
3	S	Not done	Not done	S	S	S
4*	S	Not done	Not done	S	S	S
5*	S	Not done	Not done	S	S	S

NB. R: Resistant

PS: Partially sensitive

S: Sensitive

*: From Group 2

Table 6. Antibacterial sensitivity pattern of *Streptococcus Spp.*

Isolates N=2	Benzyl penicillin	Ampicillin	Gentamicin	Chloamphe-nicol	Cefotaxime	Ciprofloxa-in
1*	S	S	Not done	S	R	S
2	R	Not done	Not done	S	R	S

NB. S: Sensitive

R: Resistant

*: From Group 1

Table 7. Antibacterial sensitivity pattern of other organisms

Isolates N=4	Benzyl penicillin	Ampicillin	Gentamicin	Chloramph-enicol	Cefotaxime	Ciprofloxac-in
Acinetobact-er Spp.	Not done	R	Not done	S	S	S
Coagulase negative staphylococ-cus	R	Not done	Not done	Not done	S	S
*Salmonella Spp.**	Not done	Not done	Not done	R	R	S
*Pseudomon-as Spp.**	Not done	Not done	Not done	Not done	S	S

NB. S: Sensitive

R: Resistant

*: From Group 1

5.3 Organisms in relation to age at the time of diagnosis

In this study, *K. pneumonia* was the commonest cause of early onset meningitis and together with *streptococcus pneumonia* were the commonest cause of the late onset of the disease (Table. 8)

Table 8. Organisms in relation to age at time of diagnosis

Bacteria	0 to 2 days	3 to 7 days	8 to 14 days	15 to 21days
K. Pneumonia	1	4		2
S. Pneumonia	1	2	1	1
Streptococcus Spp.	1			1
Mixed Growth	1	2	1	
Acinetobacter Spp.	1			
Pseudomonas Spp.			1	
CNS1		1		
Salmonella Spp.			1	
Total	5	9	4	4

5.4 Obstetric factors

In this study, the majority of mothers were aged between 20 and 30 years. Only 3 (13.6%) were teenagers in both groups.

There was no significant difference in maternal age in the two groups, *p* value = 0.67022248 (Table 9).

Table 9. Maternal age in both groups

Group	19 yrs	21 yrs	22 yrs	23 yrs	24 yrs	25 yrs	26 yrs	30 yrs	34 yrs	Total
1	1	2	0	1	1	2	1	0	0	8
2	2	0	1	1	3	2	2	2	1	14
Total	3	2	1	4	3	4	3	1	1	22

Chi -square: 5.97

Degrees of freedom: 8

P value: 0.67022248.

Table 10. Maternal parity in both groups

Group/Parity	1	2	3	4	Total
1	2	6	0	0	8
2	8	2	3	1	14
Total	10	8	3	1	22

Chi-square: 8.60

Degrees of freedom: 3

P value: 0.03505347.

All the mothers in Group 1 had a parity of less than 3 while 71% of those from Group 2 had the same parity. Group 1 had a mothers with a relatively low parity and was statistically significant, *p* value = 0.03505347

Table 11. Obstetric factors in babies in both groups

Factors	Group 1 N=8	Group 2 N=14	*P* value
PROM	0	3	0.158886860
UTH Delivery	0	6	0.012885560
Clinic Delivery	5	8	
Home Delivery	3	0	

No baby from Group 1 was born at the University Teaching Hospital and none had history of prolonged rupture of membranes (PROM). There were 3 home deliveries in Group 1 and none in Group 2. There was no statistical difference between the two groups with regard to PROM, *p* value being 0.158886860, but there was statistical difference with place of delivery, *p* value = 0.012885560

5.5 Neonatal factors in babies in both groups.

In this study the gestation age, birth weight and age at diagnosis were looked at. Tables 12 to 14 illustrate the results.

Table 12. Gestation age of the babies in the two groups

Group/Gest -ation	35	36	37	38	40	Total
1	0	2	0	2	4	8
2	1	1	1	5	6	14
Total	1	3	1	7	10	22

Chi-square: 2.57

Degrees of freedom: 4

P value: 0.63440916

Table 13. Age at diagnosis of babies in both groups

Group / Age	1	2	3	4	5	7	10	12	21	Total
1	0	0	1	0	0	2	3	0	2	8
2	5	1	0	2	4	1	0	1	0	14
Total	5	1	1	2	4	3	3	1	2	22

Chi-square: 19.12

Degrees of freedom: 8

P value: 0.0142357

Table 14. Birth weight in babies in both groups.

Group/ Weight	No weight	2.1	2.2	2.4	2.6	2.7	2.76	2.8	2.84
1	1	1	0	1	1	1	0	0	0
2	0	1	1	0	0	0	1	2	1
Total	1	2	1	1	1	1	1	2	1

Group/ Weight	3	3.1	3.2	3.3	3.5	3.7	3.8	3.87	Total
1	1	0	0	0	0	1	1	0	0
2	0	1	2	2	2	2	0	0	1
Total	1	1	2	2	2	2	1	1	1

Chi-square: 19.84

Degrees of freedom: 16

P value: 0.2275

The average weight in Group 1 was 2.5Kg and that in Group 2 was 3Kg. There was no significant difference in the weights of the two groups, p value = 0.2275

.5.6 Clinical features in the babies in both groups

Most of the clinical features were of equal incidence in the 2 groups. Table 15 illustrates them.

Table 15. Clinical features in the babies in both groups

Clinical feature	Group 1	Group 2	OR 95% CI, p value
Fever	6	6	0.43-44.37,0.14525101
Irritability	6	5	0.57-62.57,0.07626011
Respiratory distress	2	3	0.10-14.10,0.84751638
Seizures	6	3	0.01-0.98,0.01395398
Poor feeding	7	7	0.53-199.3,0.0952528
Lethargy	5	4	0.48-42.33,0.11946676
Umbilical infection	4	1	0.83-429.20,0.01021029
Jaundice	2	0	0.00-2.38,0.12121
Bulging ant. Fontanelle	4	2	0.56-0.00,0.07039398
Vomiting	0	2	0.00-9.43,0.2621960
Hypothermia	1	2	0.00-16.79,0.90653734

5.7 Outcome in babies of both groups

50% of babies in Group 1 and 43% of those in Group 2 died. One baby from each group survived with hydrocephalus and spasticity (see Tables 16,17and 18).

Table 16. Outcome in babies of both groups

Outcome	Group 1	Group 2	OR 95% CI, *p* value
Discharged	4 (50%)	8 (57%)	0.09-0.03,0.74618831
Discharged with CNS deficit	1 (12.5%)	1 (7%)	0.0084.65,0.67415022
Died	4 (50%)	6 (43%)	0.17-11.00,0.74618831
Total	8 (100%)	14 (100%)	

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Table 17. Outcome in relation to organisms

Organism	Total number	Died
Klebsiella pneumonia	7	2 (29%)
Streptococcus pneumonia	5	2 (40%)
Streptococcus Spp.	2	1 (50%)
Mixed growth	4	3 (75%)
Acinetobcter Spp.	1	0 (0%)
CNS1	1	0 (0%)
Pseudomonas Spp.	1	1 (100%0
Salmonella Spp	1	1 (100%)

Table 18. Mortality in the two Groups

Group	Died	Alive	Total
1	4	4	8
2	6	8	14
Total	10	12	22

OR 955 CI: 0.17-11.00

P value: 0.74618831

5.8 Duration of stay

Table 19 illustrates the duration of stay in hospital for both groups. There was no statistical difference between the two groups with regard to this, p value = 0.23651157.

Table 19. Duration of stay in both groups

Days/ Group	1	10	14	21	22	23	25	27
1	0	1	0	1	0	0	0	1
2	1	0	1	0	2	2	2	0
Total	1	1	1	1	2	2	2	1

Days/ Group	28	29	3	4	7	9	Total
1	0	1	1	0	2	1	8
2	1	0	2	2	1	0	14
Total	1	1	3	2	3	1	22

Chi-square: 16.24

Degrees of freedom: 13

P value: 0.23651157

CHAPTER SIX

6.0 DISCUSSION

In this study, 5% of the neonates presenting to the institution with a provisional diagnosis of septicaemia had confirmed meningitis, prevalence of 0.056 in Group 1 (General Paediatric Wards) and 0.046 in Group 2 (NICU). This is similar to that found in other studies [44,45].

With regard to aetiology, it is of interest to note that, despite the differences in the mean age groups at diagnosis in the two groups, that is 11.1 in Group 1 and 3.8 in Group 2 (p value = 0.0142357) there was no significant difference in both groups in relation to organisms isolated, p value = 0.45211586. *Klebsiella pneumonia* was the commonest organism isolated. Studies done on the disease in other countries have demonstrated that the organism is one of the leading causes of neonatal meningitis [6,57,74]. *Streptococcus pneumonia* was the second commonest organism isolated. In a study done in Lusaka at UTH in the 70s, the organism was the commonest isolated in neonates [28]. It is rarely isolated elsewhere [76]. In some countries its incidence is on the increase presenting with a lot of therapeutic difficulties [83]. The *streptococcus* species grown were not typed. Typing of the species was going to help in the analysis as for example *Streptococcus agalactiae* strains are a common cause of neonatal sepsis [52]. No *GBS* was isolated and this is similar to other studies done in other countries other than the U.K. and U.S [6,7]. During the study, one case of *Salmonella Spp., Pseudomonas Spp., CNS1* and *Acinetobacter Spp.* were

isolated. These organisms have been isolated in other studies in other developing countries [44]. *Salmonella* meningitis is very rare and difficult to treat despite adequate appropriate drugs being used [58,70]. *CNS1* is frequently isolated from blood cultures of critically ill neonates [71].

63.6% of cases were early onset (meningitis was diagnosed within 7 days) with *K. pneumonia* the commonest organism isolated (22.7%)

K. pneumonia had 100% sensitivity to ciprofloxacin, 50% to cefotaxime and 40% to chloraphenicol. The only sensitivity done against gentamicin was sensitive. It was 100% resistant to ampicillin. Most of the studies done have shown the organism is 100% sensitive to cefotaxime and that there is no role for use of ampicillin for it [2,6,44].

S. pneumonia was 100% sensitive to chloramphenicol and ciprofloxacin, 75% sensitive to benzyl-penicillin and cefotaxime. One isolate was partially sensitive to benzyl penicillin and the isolate subjected to sensitivity against ampicillin was sensitive.

Streptococcus species were 100% sensitive to ciprofloxacin and chloramphenicol but 100% resistant to cefotaxime. It would be better if the species were typed so that the exact organism is identified. One isolate of the species was sensitive to benzyl penicillin and the other was sensitive to ampicillin. Perhaps there is still a role of peniciilins in the treatment of meningitis caused by streptococcus in our environment. Studies done in other countries show increasing prevalence of penicillin-resistant *pneumococci* [83].

Acinetobacter Spp., CNS1, and *Pseudomonas Spp* were all sensitive to cefotaxime and ciprofloxacin whereas *Salmonella Spp* was sensitive to only ciprofloxacin. This demonstrates the difficulty in treating salmonella meningitis in neonates [58].

Only 3 (13.6%) of mothers in both groups were teenagers. There was no significant difference in the ages of the mothers in two groups, $p = 0.67022248$. All the mothers in Group 1 had a parity of 2 or less, whereas 71% of mothers in Group 2 had the same parity. All the mothers in Group 1 were of lower parity compared to those in Group 2. This was statistically significant, p value being 0.03505347. Studies reveal that neonatal meningitis is more likely to occur in younger mothers and of lower parity. In this study, it is evident that most of the mothers were above 20 years of age (86%) and that most of them were of low parity. Young mothers and those with low parity have a higher likelihood of having babies with the disease [1,2,16].

All 22 babies were born by spontaneous vaginal delivery (SVD) and none had instrumental delivery.

There was no statistical difference between the two groups with regard to premature rupture of membranes (PROM), p value = 0.158886860. Neonatal meningitis is associated with PROM, instrumental delivery and spontaneous vaginal delivery. The infection is acquired in early onset meningitis from the maternal genital tract and late onset infection acquired mostly from interventions perinatally.

50% of babies in Group 1 were male while 71% of babies in Group 2 were male. There was no statistical difference in sexes in the two group, $p = 0.31485395$.

36% of all the babies were of less than 37 weeks gestation, but the gestation of the babies in the two groups was not statistically different, p value = 0.63440916. The mean age at diagnosis was higher in Group 1 than in Group 2, (p value = 0.0142357).This implies that perhaps Group 1 had less maternally acquired meningitis than Group 2.

40% of all the babies were less than 2.5Kg but there was no statistical difference in the weights of the babies in the two groups, $p = 0.2275$. Low birth weight and prematurity are all associated with neonatal meningitis [1,2,3]. In this study no group had more low birth weight or preterm babies than the other.

The commonest clinical feature in all the babies was poor feeding (6.36%) and fever (5.6%). Seizures and umbilical sepsis were the only features which were statistically different in the two groups, $p = 0.01395398$ and 0.01021029 respectively. There were more babies with seizures and umbilical sepsis in Group 1 compared to those in Group 2. The rest of the clinical features were not statistically different. It's important to note that these features are non-specific [1,2,16,51].

There was high case fatality rate in *streptococcus pneumonia* (50%) and *streptococcus* Spp. (40%). *K. pneumonia* despite being the most prevalent organism had a lower case fatality rate (29%). *Streptococcus pneumonia* produces very serious sepsis in neonates [83]. The mortality rate for *K. pneumonia* is similar to that found in other studies [74]. 75 % of babies with mixed growth died while the baby with CNS1 was discharged. The baby who had *pseudomonas Spp* and the other with *salmonella Spp.* died, constituting 100% mortality for each organism. Short duration of stay was associated with high case fatality rate. There was no statistical difference in the case fatality rates in the two groups, p value = 0.74618831. The case fatality rates were similar to those of other studies [28,44].

CHAPTER SEVEN

7.0 CONCLUSION

In the period 1st March 2002 to 28th February 2003, 5 % of neonates who had LP done at UTH as part of a sepsis screen had proven meningitis by CSF culture. *K. pneumonia* was the most prevalent organism isolated followed by *S. pneumonia*. *GBS* and *E. coli* were not isolated during the study period implying perhaps that the two organisms are not an important cause of neonatal meningitis at UTH. It is important to note that there was no difference statistically between the two groups with regard to the isolated organisms. The sensitivity pattern varied, but it is evident from this study that there is emerging resistance to cefotaxime an antibacterial that is recommended worldwide making, ciprofloxacin the only alternative. Analysis of the associated factors and outcome reveals that there is no difference statistically between the two groups meaning that the two groups should be treated as one group. It was also evident in this study that the case fatality rates were similar to that of studies done elsewhere.

7.1 RECOMMENDATIONS

1. Studies like this one should be an on-going activity on our NICU so that changing aetiological patterns of septicaemia and/or meningitis and their resistance are constantly updated.
2. From the results of this study, I recommend ciprofloxacin as the first line of treatment for neonatal meningitis.

7.2 STUDY LIMITATIONS

1. Not all babies with sepsis had an LP done as some parents refused the procedure.

2. Failure or success of an LP depended upon the attending doctor's experience.

3. Non-availability of certain discs for sensitivities in the laboratory.

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QUESTIONAIRE

History

1. Study No.: 2. Name: 3. File No.: 4. Date of Interview:

5. Date of birth: 6. Time of birth: 7. Sex: M/F 8. Bwt: 9. Place of birth:

10. Apgar score: at birth: at one minute: at five minutes:

11. Place of referral: 12. Reason for admission:

13. Age at Diagnosis: 14. Age of mother: 15. Gravidity: 16. Parity:

17. ANC: i. RPR 18. Residence:

ii. UTI

iii.other:

18. MOD: 19. Instrumental delivery: Y/N 20. PROM: Y/N

21. Birth trauma: Y/N 22. Arterial/Umbilical catheterisation: Y/N

23. Other surgical procedures: Y/N - specify

24. Duration of illness: 25. Fever:Y/N/Hypothermia 26. Refusing to suck: Y/N

29. Vomiting: Y/ N 29. Difficulty in breathing: Y/N 29. Irritability: Y/N

30. Bulging AF: Y/N 31. Lethargy: Y/N 32. Umbilical discharge/redness: Y/N

33. Seizures: Y/N

Examination:

34. Temp: C 35. Pallor: A/P 36. Jaundice: A/P 37. Cyanosis: A/P 38. Head C.:

39. Petechial rash: A/P 40. Umbilical sepsis: A/P

41. Neonatal reflexes: Grasp: A/P Respiration: Rate & type

Moros: A/P

Sucking: A/P

42. Bulging AF: Y/N 43. Seizures: A/P 44. Focal neurological signs: A/P

45. LMP;gestation by dates:

46. Clinical gestation age: 47. CNS malformations:

48. Antibacterials: Prior to admission

From admission

CSF Findings:

49. Microscopy:

Appearance

Cells- wbcs:

- rbcs:

Organisms: *G.B.S.* *S. pneumonia* *E. coli* *L. monocytogenes*

K. pnuemonia *S. aureus* Others Mixed

50. Culture: *G.B.S.* *S. pnuemonia* *E. coli* *L. monocytogenes*

K. pnuemonia *S. aureus* Others Mixed

51. Sensitivity:

Immediate outcome:

52. Head circumference on admission: cm. on discharge: cm. 53. Tone:

54. Convulsions: A P 55. Cranial nerve palsies: A P

56. Utrasonography (where done): 57. Date of discharge or death:

58. Duration of stay: