# ACUTE ENCEPHALOPATHIES IN UNDERFIVE CHILDREN ADMITTED IN PAEDIATRIC WARDS OF MUHIMBILI NATIONAL HOSPITAL, DAR ES SALAAM TANZANIA 2009.

By

Namala P. Mkopi, MD (UDSM)

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A dissertation submitted in partial fulfillment of the requirements for the degree of Master of Medicine in Pediatrics and Child Health of the Muhimbili University of Health and Allied Sciences.

2009

## CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance a dissertation entitled **"ACUTE ENCEPHALOPATHIES IN UNDERFIVE CHILDREN ADMITTED IN PAEDIATRIC WARDS OF MUHIMBILI NATIONAL HOSPITAL, DAR ES SALAAM TANZANIA 2009"** in partial fulfilment of the requirements for the degree of Master of Medicine (Paediatrics and Child Health) of the Muhimbili University of Health and Allied Sciences.

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Prof. Karim P. Manji
(Supervisor)

Date 12th October, 2009

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Prof. C.R.J.C. Newton
(Supervisor)

Date 23/10/2009.

## DECLARATION AND COPYRIGHT

**I, Namala Patrick Mkopi,** declare that this dissertation is my own original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

Signature 

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## DEDICATION

To my family

To all children who need us to speak for them.

## ABSTRACT

**Background:**

Acute Encephalopathy (AE) due to Central nervous system infections are the common cause of non-traumatic altered level of consciousness in underfive children and has high mortality rate. Cerebral Malaria and Acute Bacterial meningitis are commonest documented causes and remains the leading cause of mortality with high case fatality rate. There is need to identify other possible causes and whether HIV has influenced their outcome, besides identifying risk factors in the outcome of AE in children.

**Objectives:**

To determine the cause of acute encephalopathy in children admitted in paediatric wards and risk factors for poor outcome.

**Methodology:** Determination of causes and risk factors for poor outcome in a descriptive hospital based study of 107 consecutively enrolled children aged two to sixty months with altered level of consciousness. Cerebrospinal fluid for biochemistry and microbiology was obtained, blood for culture, malaria microscopy, random blood glucose, chemistry and HIV antibody test or HIV-DNA PCR when indicated was taken. Data were recorded on daily coma score and other clinical features, laboratory findings, underlying disease and the children outcome.

**Results:** During this study, a total of 107 children aged 2 -59 months were recruited of whom, 55 (51.4%) were males. Thirty nine percent of children were admitted in their first three days of illness. Eighty four (78.5%) children received treatment prior admission. Acute bacterial meningitis was found in 44(41.12%) children while

cerebral malaria was in 32(29.91%). *Haemophilus influenzae* was observed microscopically in 77.8% of children; however, the positive CSF culture was 3.7% of all children. Children below 12 months were 34 (32%) and they were more prone to ABM (50%) while those above 24 months were prone to CM (57.58%), so age had significant correlation with ABM and CM distribution (p=0.003). Approximately 10% of children were discharged with neurological sequelae. Mortality rate was 60.7% in this study. Unfavorable prognostic indicators were; duration of illness prior admission (OR 5.35; CI 1.15-24.95), age less than 12 months (OR 4.08; CI 1.51-10.91), deep coma on admission (OR 13.42; CI 2.77-64.88), status epilepticus (OR 10.5; CI 1.31-83.9) and abnormal posture (OR 26.43; CI 3.40-205.60).

**Conclusion:** The most common cause of acute encephalopathy is acute bacterial meningitis followed by cerebral malaria with a high mortality rate. *Haemophilus influenzae* has been the commonest cause of acute bacterial meningitis. The use of antimalarial and antibiotics prior to admission may have hampered the detection of organisms and hence underestimate the burden of cerebral malaria and bacterial meningitis as well as co-morbidity.

**Recommendation:** With high mortality rate in this study, a larger study should be conducted to establish factors both at the community and health facility level to speed up presentation and early treatment of children with acute encephalopathy.

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**ABBREVIATIONS**

| | |
|---|---|
| ABM | – Acute Bacterial Meningitis |
| AE | – Acute Encephalopathy |
| AIDS | – Acquired Immuno-Deficiency Syndron |
| APCU | –Acute Paediatric Care Unit |
| BCS | – Blantyre Coma Scale |
| CFR | - Case Fatality Rate |
| CM | – Cerebral Malaria |
| CNS | – Central Nervous System |
| CPL | – Central Pathology Laboratory |
| CSF | – Cerebral Spinal Fluid |
| Hib | – *Haemophilus influenzae* type b |
| HIV | – Human Immunodeficiency Virus |
| ICP | – Intracranial Pressure |
| LP | – Lumbar Puncture |
| MNH | – Muhimbili National Hospital |
| MUHAS | – Muhimbili University of Health and Allied Sciences |
| PCR | – Polymerase Chain Reaction |
| PMN | – Polymophonuclear |
| SIADH | – Syndrome of Inappropriate Anti-Diuretic Hormone Secretion |
| SOP's | - Standard Operating Procedures |
| WHO | – World Health Organization |

# .0 INTRODUCTION AND LITERATURE REVIEW

## .1 BACKGROUND

Acute encephalopathy (AE) is an acute generalized disorder of cerebral function. Acute encephalopathies are important causes of neurodisability, and have high mortality rate. It has wide range of primary aetiologies including central nervous system (CNS) infections and toxic-metabolic conditions[1]

Children with AE commonly present with overlapping signs and symptoms such fever, seizures, status epilepticus and loss of consciousness. [2,3] Acute encephalopathy carries a high case fatality of up to 50%. [4] However, for those who survive they may either develop neurologic disability or recover completely.[5,6]

In sub-Saharan Africa, the major causes of AE include acute bacterial meningitis, cerebral malaria, viral encephalitis and metabolic-toxic encephalopathy. Other causes do exist such as HIV encephalopathy and fungal encephalopathy. Co-morbidity is common. [1,7-9] However, in the majority of cases of AE in sub-Saharan Africa, it is difficult to differentiate between these major causes as their clinical picture/presentation tends to overlap; so diagnosis is based on exclusion of the other causes. [8,9] Even with appropriate facilities some causes especially viruses are difficult to diagnose by culture and in some studies indicate difficulty in isolating viruses despite the presence of other indicators of viral infection. [10,11]

Treatment of an individual case usually depends on the cause of AE. But supportive measures can be given irrespective of the cause. [11-13] The outcome depends on multiple factors including; aetiology, severity of the illness, age of the child, nutritional status as well as HIV status of the patients.[1,14,15]

## Acute Bacterial Meningitis

Acute bacterial meningitis (ABM) is a major cause of death and disability worldwide with more than 1 million cases and 200,000 deaths are estimated to occur annually.[16] Half of all childhood deaths from meningitis worldwide occur in sub-Saharan Africa. Bacterial meningitis is ten times more common in children in developing than in developed countries. In resource poor countries the case fatality rate (CFR) is high (12–50%) whereas it is about 5% in developed countries. [14,17,18] A study done by Kalokola *et al.* in Tanzania found a CFR of 51.9%.[19]

*Neisseria meningitidis, Haemophilus influenzae type* b (Hib) and *Streptococcus pneumoniae* are major causative agents of bacterial meningitis in children. Clinical features of meningitis usually overlap with those of malaria. These include impaired consciousness, seizures, fever and opisthotonus posture. Thus it is difficult to differentiate between meningitis and malaria based on clinical findings alone.[2,17,18,20,21] However, immediate complications include septic shock, disseminated intravascular coagulation and syndrome of inappropriate antidiuretic hormone secretion (SIADH). [7]

Acute bacterial meningitis remains an important cause of neurologic sequelae in children in developing countries. A third of all survivors of ABM are left with sequelae.[14,18] In some cases neurological sequelae tend to occur when there is delay in diagnosis and treatment and such situations are common in developing countries like Tanzania. [22]

The common neurological sequelae that have been described in childhood meningitis include neuromotor impairment, learning disorders, ocular and visual problems, hearing loss, language and speech disorders. Others are cranial nerve deficits, seizure disorders, hydrocephalus, brain abscess and behavioural problems. [22]

In the majority of hospitals in sub-Saharan Africa, the laboratory facilities to confirm the diagnosis are inadequate. Therefore, the diagnosis of childhood ABM is likely to be missed in a third of cases at district hospitals.[23] Although, gross examination of cerebrospinal fluid (CSF) which shows turbid fluid could be indicative of meningitis. This is due to lack of adequate and reliable laboratory resources.

However, the early recognition of ABM among children who are more severely ill warranting hospital admission seems to be more problematic. At a tertiary centre in Malawi, meningitis was included during admission in the differential diagnosis of 42% of the cases subsequently proven bacterial meningitis cases. Most of cases were initially thought to have malaria. Similarly a study done at Kilifi-Kenya, found that clinicians correctly included a diagnosis of meningitis at the initial clinical assessment in 30% of admissions with final diagnosis of meningitis.[18]

Cerebrospinal fluid examination is essential in the aetiological diagnosis of acute bacterial meningitis and is highly recommended to improve management and prognosis. Culture-confirmed diagnosis of CNS infections is hindered by the failure to isolate bacteria following early antibiotic treatment. Examination of the CSF (biochemical finding and Polymophonuclear leukocyte count) may be helpful to differentiate between acute viral and acute bacterial meningitis. However, culture is the best method to detect the aetiological agent of acute bacterial infections. [23-25] Culture facilities are expensive and difficult to maintain.[23] So, greater gains could be achieved with facilities for accurate leukocyte counting, glucose measurement and also looking for turbidity.

## 1.3 Cerebral Malaria

Cerebral malaria (CM) is the most severe complication of *Plasmodium falciparum* infection and is a major cause of acute non-traumatic encephalopathy in tropical countries. Prevalence of CM varies by geographic region and by intensity of transmission of malaria.[2,26-30]

*Plasmodium falciparum* is a leading cause of ill health worldwide. About 2 billion people are exposed to falciparum malaria annually resulting in over 500 million clinical attacks.[28] WHO estimates about 1.5 to 2.7 million deaths and other studies reports to be about 1 million every year.[31] Data from the 1990s suggested that as many as 90% of all malarial cases and 90% of deaths take place in sub-Saharan Africa.[32] This is where levels of endemicity are high, and severe disease and mortality occur primarily during infancy and

early childhood.[26,32-34] Cerebral malaria is among major causes of mortality among children under-five years in malaria endemic areas. Its mortality rate varies, in some studies from 10% - 30% and 10% - 50% in others.[4,26,27,33,35-38]

The World Health Organisation defines cerebral malaria if a patient is unable to localise a painful stimulus, has a peripheral asexual falciparum parasitaemia and no other causes of an encephalopathy could be found.[32] The most common causes that can be excluded are bacterial meningitis, hypoglycaemia, and viral encephalitis with a pleocytosis. In malaria endemic areas, CM is a diagnosis of exclusion. Many infective, traumatic and metabolic processes cause coma and in malaria endemic regions, some of these patients may have incidental malaria parasitaemia. [32]

Clinically patients with CM present with coma, seizure and fever. These symptoms may be accompanied with, severe anaemia and/or respiratory distress, hypoglycaemia and lactic acidosis, when present is associated with high mortality. Decorticate, decerebrate and opisthotonus posturing is common.[27,29,36]

In CM, children are left with neuro-cognitive sequelae. In a meta-analysis which used studies with a similar definition of CM, 10.9% children with cerebral malaria were discharged with clearly definable neurological deficits.[36] Recent studies have shown that the prevalence is much higher, with 24% of children found to have neuro-cognitive impairment when assessed 3-7 years later. This shows the magnitude of the burden in malaria endemic areas, suggesting that at least 250,000 children will develop persistent neuro-cognitive impairments from CM in sub Saharan Africa per year.[4]

The most common neurological deficits include motor impairments (hemiparesis, quadriparesis), isolated cranial nerve deficits, ataxia, cortical blindness, severe learning difficulties and aphasia. Some deficits are transient (*e.g.* ataxia), whilst others *e.g.* hemiparesis, although might improve over months, may not resolve completely.[2] Recently, the risk of developing epilepsy later on in children who had CM has been demonstrated.[3]

Neuro-cognitive sequelae of CM are associated with protracted seizures, prolonged and deep coma, hypoglycaemia, and severe anaemia in some studies, but not in others. The

consistent association found between prolonged seizures or hypoglycaemia and neuro-cognitive impairment suggests hippocampal damage, which may manifest as memory impairment and complex partial seizures at a later date. Other smaller studies have shown an association between the development of sequelae and pathophysiological processes such as raised Intracranial Pressure (ICP). [2,26,39-41]

Cerebral malaria due to *Plasmodium falciparum* is treated with antimalarial agents and in some centres where facilities are available, the use of exchange transfusion is employed.[7]

## 1.4 Viral encephalopathy

Acute infection of the brain parenchyma can be caused by viruses: most commonly *Herpes simplex virus* 1 and 2, arboviruses, enteroviruses, cytomegalovirus, varicella zoster, rabies, *Epstein–Barr*, measles, mumps and rubella. In this era of HIV the acute encephalopathy in an HIV infected child may be due to HIV itself as it is known to be one of the viral causes of encephalopathy or due to other opportunistic infections. HIV is known to cause acute as well as progressive and static encephalopathies.[14,42]

Viral encephalopathy in a study of 338 children less than three years was found to have high CFR of up to 34% . [43]

Children with viral encephalopathy present with fever (not invariable) or meningism, depressed level of consciousness, seizures, or focal neurological deficit. [44]

About half of the survivors develops motor dysfunction; well over third had neurological dysfunction; and almost a fifth had behavioural, self care, and sensory dysfunction. Mortality and morbidity is high in children with multisystem disease. [43]

Clinical features are helpful in predicting the outcome of children with viral encephalopathy. Young age, low conscious level, abnormal occulocephalic responses are pointers to a poor prognosis.[45]

Treatment of viral encephalopathies is usually supportive. However, acyclovir is useful adjunct for herpes simplex virus, varicella zoster and cytomegalovirus. Acyclovir is relatively non-toxic and therefore should be started if there is clinical suspicion of herpes simplex virus or varicella zoster infection. However it is not often used in sub-Saharan Africa because of the expense. Immunization is important in preventing viral encephalitis due to measles, mumps, rubella and polio[7].

### 1.5 Metabolic Encephalopathy

This is the abnormality of the brain function which is reversible; it is caused by the process which is extracerebral in origin. These processes usually involve some metabolic derangements (electrolytes, renal function or hepatic dysfunction), some toxic exposure (drugs, alcohol, medicines, etc) or systemic toxic states (sepsis, for example). Therefore, in metabolic encephalopathy, there is diffuse cerebral dysfunction.[9]

Clinical signs in metabolic encephalopathies may be divided into diffuse neurological dysfunction signs and focal neurological signs. Diffuse signs predominate and they may be accompanied by mostly less expressed focal signs depending upon the severity of encephalopathy. In the group of diffuse signs especially in early stages confusion and slight cognitive disturbances preponderate but condition can deteriorate to altered consciousness, confusional states and psychomotor hyperactivity and autonomic dysfunctions. In more severe cases global brainstem signs with oral and facial automatisms, pathological reflexes such as grasp reflexes, changes in spontaneous movements, tremor and abnormalities of muscle tone (decorticate and decerebrate posturing) are found.[9,46]

Signs of metabolic encephalopathy may be an early indication of developing complications. This is a need for careful control of the clinical neurological status of the patients.[9,46] Investigations performed during the acute illness (blood sugar, arterial blood gases, plasma ammonia, blood lactate, plasma ketones, and liver functional tests) may identify those patients in whom a metabolic disorder is likely.

Metabolic acidosis is common in sick children regardless of the cause and in most is secondary to lactic acidosis generated because of poor tissue perfusion.[12] Metabolic encephalopathy is a condition that is in principle reversible upon early treatment. Reversibility of metabolic encephalopathy relates to successful treatment of systemic dysfunction. Treatment of these conditions is largely supportive, with especial attention to the management of cerebral perfusion pressure.[34,46,47]

## 1.6 CLASSIFICATION OF ENCEPHALOPATHIES

In this study Acute Encephalopathy was classified into four main groups;

i. Acute Bacterial Meningitis (ABM).
ii. Cerebral Malaria (CM).
iii. Encephalopathy with pleocytosis ≈ viral encephalopathy, not ABM or CM.
iv. Encephalopathy without evidence of ABM or CM and without pleocytosis ≈ metabolic encephalopathy.

## 1.7 EXPECTED OUTCOMES OF AE

i. Complete recovery at discharge.
ii. Development of sequelae at discharge (Neurological Deficit).
iii. Death.

## 1.8 DEFINITIONS

**1.8.1 Acute Encephalopathy:-** Acute encephalopathy is a rapid decrease in conscious level (over hours or days), not secondary to epileptic seizures nor syncopal episodes

**1.8.2 Acute Bacterial Meningitis: -** Acute Bacterial Meningitis is defined as acute febrile encephalopathy with identification of microorganisms from the CSF culture; microorganisms seen by Gram staining or presence of 2 or more of the following abnormalities in CSF:

**a)** Polymophonuclear leucocytosis
**b)** Glucose < 2/3 of blood sugar
**c)** Elevated proteins > 0.43 mmol/l

**1.8.3 Cerebral Malaria: -** To exclude incidental parasitaemia and systemic causes of impaired consciousness, the WHO has suggested strict criteria for CM: *a patient who is unable to localise a painful stimulus, has a peripheral asexual falciparum parasitaemia and no other causes of an encephalopathy could be found.* For the purpose of this study, CM is considered when a patient is unconscious, has a peripheral asexual falciparum parasitaemia and no other causes of AE could be found.

**1.8.4 Encephalopathy with pleocytosis (Viral Encephalitis):-** Viral encephalopathy is defined as acute febrile encephalopathy with CSF pleocytosis with lymphocyte predominance (>5 cells/$mm^3$) and absence of bacteria on direct microscopy, culture and where no other alternative diagnosis was identifiable.

**1.8.5 Metabolic Encephalopathy: -** Disorders in which a disturbance of cerebral function results from failure of some other organ system and there are evidence of metabolic derangement commensurating with the clinical picture.

**1.8.6 Short term outcome** of AE: - for the purpose of this study, these are the observations made after recruitment into the study to the time where the patient is discharged from the study; these include death, development of neurological deficit/sequelae and complete recovery at discharge.

**1.8.7 Blood glucose levels.**

**Normal glycaemia** is defined as whole blood glucose concentration of between 3.5mmol/L to 7.5mmol/L.

**Hypoglycaemia** is defined as whole blood glucose concentration of less than 3.5mmol/L.

**Hyperglycaemia** is defined as whole blood glucose concentration of more than 7.5mmol/L.

**1.8.9 Haemoglobin levels.**

**Normal haemoglobin** is defined as haemoglobin level between 11.5 to 15.6 g/dl

**Mild anaemia** is defined as haemoglobin level between 10.0 to 11.4 g/dl

**Moderate anaemia** is defined as haemoglobin level between 7.0 to 9.9 g/dl

**Severe anaemia** is defined as haemoglobin level of less than 7.0 g/dl

## 1.9 PROBLEM STATEMENT

Children admitted with acute encephalopathies are initially presumptively treated as cases of cerebral malaria and acute bacterial meningitis regardless of the blood film and CSF examination results. Only in few instances other forms of AE are considered often after poor response to anti-malarial drugs and antibiotics. However, not all forms of AE will respond to concurrent use of antibiotics and anti-malarial drugs.

In many parts of sub-Saharan Africa it has been observed that children are poorly investigated and procedures like examination of CSF are not being done in all cases where it is indicated. Due to lack of diagnostic facilities and shortage of trained health care providers the true magnitude of AE in terms of aetiological agents and the respective treatment outcome in many parts of the country remains unknown. As a result most of encephalopathies receive blind empirical treatment without establishing the cause. This in part may be contributing to the high CFR among patients with acute encephalopathy.

Moreover the magnitude of HIV in sub-Saharan Africa is high; and the presentation, diagnosis, complications and outcome are difficult to predict as HIV itself can be the sole cause, as well as a precipitating factor in other forms of encephalopathies, or opportunistic infection.

## 1.10 RATIONALE OF THE STUDY

Acute Encephalopathies are common in sub-Saharan Africa and in Tanzania, and are associated with a high morbidity and mortality.

In this study, the principle investigator wanted to document the major aetiological causes of AE in children under five years in Dar es Salaam and the contribution of cerebral malaria and acute bacterial meningitis as causes of AE in this setting.

The study documented the difference in the outcome of each group category of AE in this age group admitted in the paediatric wards.

The study provided useful baseline data on causes and outcome of various forms of AE.

The description of the different causes and outcome of AE is going to improve decision making pertaining to treatment modalities and prediction of the outcome of these patients.

## 2.0 STUDY OBJECTIVES

**Broad Objective**: To determine the cause of acute encephalopathy in children admitted in paediatric wards and risk factors for poor outcome.

**Specific Objectives: were to determine;**

1. The distribution of causes of acute encephalopathy by age and sex.
2. The short term outcome of acute encephalopathy by age.
3. The risk factors associated with mortality in children with acute encephalopathy.
4. The HIV sero-status among children admitted with Acute Encephalopathy.

## 3.0 METHODOLOGY

**3.1.1** **Study Design:** Descriptive hospital based study

**3.1.2** **Study sites:** This study was conducted in Paediatrics wards of Muhimbili National Hospital (MNH), in Dar Es Salaam, Tanzania. MNH is a tertiary hospital where children from public hospital are referred to.

MNH is the largest hospital in the country with more than 1000 beds. It serves as a National referral and University teaching hospital, as well as a primary and referral hospital for a population of approximately 3.6 million in the Dar es Salaam. It is located in West Upanga, Ilala Municipal, Dar es Salaam city (altitude < 100 m). The Paediatric department has two general paediatric wards and one unit each for Acute Paediatric Care Unit (APCU), Diarrhoeal Diseases, Severe Malnutrition and Neonatal Special Care. The total number of admission is about 5,000 annually and mortality rate of about 15% in the general wards. In APCU the mortality rate was 60.8% malaria being the common cause second pneumonia as noted in the 2006 annual report. [48]

**3.1.3** **Study Populations:** All children admitted to the paediatric wards from June 2008 to February 2009 were considered and those aged 2 – 59 months were assessed for inclusion into the study.

**3.1.4** **Inclusion criteria**:

i. All children admitted with impaired level of consciousness.
ii. Those found with hypoglycaemia on admission and one hour after its correction remained with altered level of consciousness and those with persistent hypoglycaemia.
iii. All children aged two to fifty nine months inclusive.
iv. Parents/guardian who gave informed consent for the child to participate in the study.

**3.1.5** **Exclusion criteria**

i. Head trauma/injury cases.
ii. All cases of cerebral palsy and preceding neurological deficits.
iii. Parents/guardian who did not consent for their child to participate in the study.

### 3.1.6 Sample Size estimation:

The sample size was reached after calculating individual sample size of each group of encephalopathy and the largest sample size was taken to increase power of the study.

$$n = \frac{Z^2 p (100 - p)}{e^2}$$

Where; n – sample size; Z - Standard normal deviation = 1.96; p – Percentage = 10%. [49] e – Margin of error = 6% The calculated sample size was (n) = 96.

The sample size was increased by 10% (≈10) to allow for non – response, incomplete investigations and other factors that may decrease the yield of response.

Total calculated sample size was therefore **106**

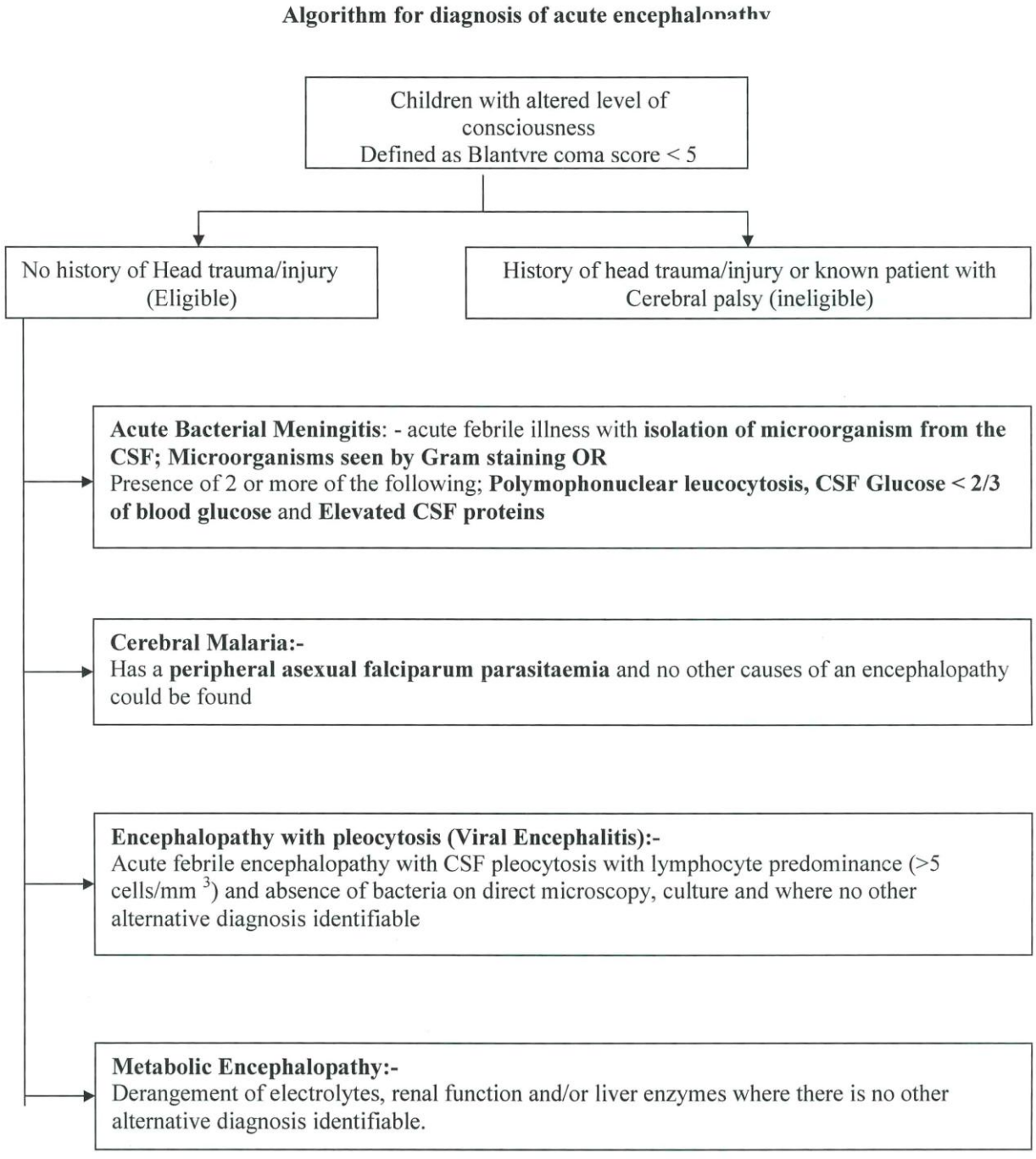
### 3.1.7 Sampling Procedure

All children meeting the inclusion criteria were consecutively enrolled into the study after parent/ guardian has given a written consent. The parent/guardian signed two consent forms that were administered by principal investigator (PI), one for participating in the study and the other for HIV testing. Recruitment of patients and sample collection were done from Monday to Friday and from 08:00 to 16:00 hours for convenience.

Patients stayed in the study from the day of admission until discharge or death.. Examination of CNS was done once daily by the PI. Monitoring of other clinical parameters was done by health care practitioners of the Hospital. To increase the recruitment of patients with acute encephalopathy sensitization was done in Municipal hospitals (Amana, Temeke and Mwananyamala) every two weeks.

After recruitment patient were seen on daily basis by the investigator until the patient was discharged or died.

**Fig 1. Algorithm**



### 3.1.8 Data Collection and Instruments

The PI assessed the eligibility of all patients admitted in the ward, administered the informed and HIV screening consent forms to all eligible patients and recruited those who fulfilled the inclusion criteria and record all the information in a standardized questionnaire designed for the purpose of the study.

The PI was responsible for taking all investigations (drawing blood and performing Lumbar puncture) and deliver them immediately to the laboratory for analysis, daily clinical assessment of the patients (physical examination) and pre- as well as post test counselling.

**Assessment**

The information obtained:
Demographic details: Age, sex, date and time of admission (appendix I).
Clinical history: The key symptoms of AE such as fever, convulsions and loss of consciousness were assessed (appendix I).
Medication history, particularly to determine previous use of antibiotics and antimalarial for the past 48 hours as some of children would have taken antibiotics and antimalarial before they are admitted in a referral hospital in Dar es Salaam.
History of being counselled and tested for HIV/AIDS was sought and whether the child is on co-trimoxazole prophylaxis or antiretroviral therapy (ART). For those whom HIV screening was not done pre test counselling for HIV/AIDS and HIV screening was done.

**Physical examination;**

A thorough clinical examination was done to every child to elicit clinical signs of AE [such as abnormal posture, neck stiffness, exaggerated reflexes e.t.c. (appendix I)] and exclude chronic CNS pathology such as cerebral palsy. The PI did physical examination on all patients. This involved examination of all systems starting with general examination, where important vital signs and hydration status were

examined. This was followed by other system examination most importantly CNS as it is the core system that was affected most in this study.

**Central Nervous System examination**

The following was examined and documented;

Higher centres where level of consciousness was determined by Blantyre coma score based on the following parameters:

| | | | |
|---|---|---|---|
| **Best Verbal response** | - | Appropriate cry | 2 |
| | | Inappropriate cry or moan | 1 |
| | | No cry | 0 |
| **Best Motor response** | - | Localise pain | 2 |
| | | Withdrawal from pain | 1 |
| | | Non-specific or no response | 0 |
| **Eye Movement** | - | Directed eye movements | 1 |
| | | Not directed | 0 |

The maximum score is five when the patient is fully conscious and any score below this was regarded as impaired consciousness. However, children of less than eight months cannot consistently localise painful stimulus. For the purpose of this study all children were in discriminatively assessed for depth of coma.

The Posture of the patient was observed and documented; described as:

Normal, Decerebrate, Decorticate, Opisthotonus or Hemiplegic.

Signs of meningeal irritation were elicited and these were:

stiff neck, positive Kernigs sign, retracted neck bulging fontanel.

Presence of bruxism.

Pupil size was examined and noted as constricted, midposition or dilated.

Pupil reaction to light (use a bright torch light) was assessed and recorded as none, sluggish or brisk.

Vertical occulocephalic reflex (moves head briskly up and down) was assessed and documented as absent or present.

Horizontal occulocephalic reflex (Move head side to side) was assessed and documented as None, Minimal or Full.

Muscle Tone of both upper and lower limbs was assessed and recorded as Decreased, Increased or Normal.

Tendon Reflexes (deep) were tested and recorded as Decreased, Increased or Normal.

Planter reflex was tested and recorded as up going, down going or Equivocal.

CNS examination was done on the day of admission and on the day of discharge to ascertain and document neurological status of the study participant.

Other systems were systematically examined (appendix I).

## 1.9 INVESTIGATIONS

**CSF specimen collection and analysis;**

**Position**

The child was placed at the edge of a firm examination table and gently maintain in position with the neck flexed and the knee drawn towards the chest.

**Site**

LP was performed at the line joining the superior portion of the iliac crest with the spine. This point corresponds with the spinuous process of L4. The needle was inserted at L3-L4.

**Procedure for lumbar puncture**

The patient's back was cleansed with povidone-iodine solution and then draped. Under strict aseptic technique lumbar puncture was done, whereby CSF was collected into two vacutainer. One was sent for microbiological and another for biochemical analysis.

**Fluid Analysis**

Analysis of CSF was done within one hour so the transport to the laboratory was done just after finishing the procedure. The specimen collected was first examined by the investigator with naked eyes for its appearance, and classified as turbid or clear.

The first vacutainer was for microbiology examination where gram stain, Ziehl Nelson stain, Indian ink was done; cell count were also done where WBC (total and differential) count and RBC count was done. Also culture and sensitivity was done.

The second vacutainer was for biochemistry where CSF protein and glucose were measured.

**Macroscopic examination**

As soon as the CSF reaches the laboratory, it was examined by naked eye and its appearance was noted and reported as:

Clear, turbid or cloudy, and if contains blood.

Normal CSF appears clear, bright and colourless.

Turbid or cloudy CSF indicates presence of pus cells, suggestive of acute pyogenic bacterial meningitis.

Blood in CSF may be due to traumatic lumbar puncture or less commonly to haemorrhage in the CNS.

**Microscopic examination**

**Cell counting:** this was done by using an improved Neubauer chamber. The CSF was diluted in isotonic 0.1% toluidine blue by 1:1. The counting chamber was carefully filled with well mixed diluted CSF by using capillary tube. After two minutes (for cells to settle), the cells were counted microscopically. Focus the cells and rulings using the 10x objective with the condenser iris closed sufficiently to give good contrast. If the mixture of both lymphocytes and polymophonuclear neutrophils were present, the percentage of each type of cell was estimated. When red cells were seen, this was reported. The cell count was done in the large four squares labelled **L** as shown in fig.2.

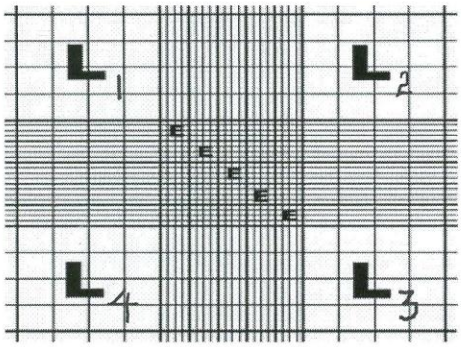



**Fig 2**. Improved Neubauer ruled chamber. Cells are counted in the squares marked **L1, L2, L3, and L4.**

Reporting – Multiply the cells counted by 5, report the number of cells per litre of CSF ([Number * 5] X $10^6$ cells/L).

**Gram staining:** It is important when the CSF contains pus cells. It may also provide useful information when CSF is unsuitable for cell counting or biochemical testing (e.g. when it is heavily blood stained).

Several drops of CSF placed on the slide and allowed to air-dry. The preparation was alcohol-fixed and gram staining technique was used.

The smear was examined under microscope for pus cells and bacteria using the 40X and 100X objectives.

Pus cells reported as many, moderate number, or few. These when found are suggestive of pyogenic bacterial meningitis.

Bacteria could be gram negative diplococci, gram positive diplococci or streptococci, and gram negative rods.

**Culture**

Culture of the CSF was done after centrifuging the sample in a sterile capped tube for 15 minutes, and the sediment was inoculated on the culture media. The CSF was cultured within one hour of collection.

**Chocolate and blood agar:** These were used for the inoculation of the specimen. Both plates were incubated in a carbon dioxide enriched atmosphere at 35 – 37 ° C for up to 48 hours, checking for growth after overnight incubation was done.

**Reporting** – NBG if there were no growth and the name of the microorganism for positive growth.

**Biochemistry**

**Protein** – the CSF protein concentration was measured and a value of 0.48 or less was considered to be normal and above this was elevated.

CSF protein is raised in most forms of meningitis

**Glucose** – the CSF glucose concentration was measure and when the value found to be less than two third of blood glucose level was considered to be low, and acute bacterial meningitis was suspected. CSF glucose level is normal in viral meningitis and cerebral malaria.

**Blood glucose**

Blood glucose was done in the ward just after the lumbar puncture. This was done by using ACCU-CHEK® Active meter. A tip of the finger was wiped with 70% alcohol and left to dry. With a lancet's finger prick a drop of blood was obtained and applied on the ACCU-CHEK Active test strip in the meter where in about five seconds a reading appears in millimoles per litre. The reading observed was recorded on the patients file and on the CSF biochemistry investigation form.

**Malaria blood slides**

Blood slide for malaria parasites (thick and thin film); this was done to get the parasite count and to identify the species.

**Procedure**

The finger was wiped clean with cotton wool lightly soaked in 70% alcohol using firm strokes to remove dirt and was let to dry. The ball of the finger was punctured with sterile lancet. The first drop was wiped away with cotton wool.

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**Thick smear**: while handling the slides by the edges, two or three drops were collected. Using the corner of the spreader, the drops of blood were spread to make an even thick film. The thick film was allowed to dry.

**Thin smear**: while handling the slide by the edges, further pressure was applied and two to three blood drops were collected. The drop was touched by the spreader and allowed the blood to run along its edges and then at an angle of 45° the spreader was pushed along the slide to make an even thin film.

Both slides were labelled using lead pencil with identification numbers of that particular child. With the investigation forms, slides were dispatched to the laboratory as soon as possible.

**Laboratory procedures**

Fixation – this is done for thin films only, methanol was used for fixation and the process takes 15 – 30 seconds.

Staining – this was done using a mixture of buffer solution (pH 7.2) and Giemsa stock solution to make 6% Giemsa solution. Staining dish was filled with staining solution where thick and thin films were placed. The blood slides were stained for 45 minutes.

After staining the thin films were washed with tap water. Thick films were carefully rinsed since they are not fixed before staining. The slides were let air dry.

Examination – two drops of emulsion oil were put on the slides and was then examined under the microscope with 100X objective for counting and identifying the malaria parasites.

Reporting - the results were reported in number of trophozoites per 200 WBC.

**Blood specimen collection and analysis**

Strict aseptic technique was observed. The child's skin cleaned with a swab soaked in 70% alcohol and allowed to dry before blood was drawn. Blood was

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taken from the anterior cubital fossa of each child using a disposable syringe and needle, a total of seven millilitres of blood were taken for all investigations using a ten cc syringe, then divided into 4 aliquots, one each for Full Blood Picture (FBP), HIV Elisa/DNA-PCR, blood culture, Serum electrolytes, liver function test and renal function test in appropriate containers.

**Blood culture:** Two millilitres of blood inoculated into paediatric blood culture bottles after changing the needle cleaning the top with 70% alcohol and allowed to dry.

In the laboratory the blood culture bottles were immediately loaded into the blood culture equipment to ensure performance efficacy. The BACTEC® 9050 system (BACTEC® 9050; Becton Dickinson) was used to process all blood cultures.

The BACTEC® 9050 system monitors carbon dioxide production released by the microorganisms within each bottle. Bottles identified as positive culture were immediately removed from the instrument and an aliquot taken for gram stain and subculture.

Bacterial isolates were identified by conventional procedures. The subcultures were inoculated on solid agars; CLED (Cystene, Lysine, Electrolyte Deficiency), blood and chocolate agars, incubated aerobically at $37^0$c for 18-24 hours. After 24 hours of incubation colonies were identified based on characteristic morphology, gram stain appearance and standard commercially prepared biochemical tests as described in Cowan and Steel's manual for identification of bacteria.[82] The isolates were stored on nutrient agar slopes at room temperature and in prepared freezer medium of Tryptone Soya Broth with 15% Glycerol (TSBG) and stored at $-70^0$C for further identification and testing later on.

Antimicrobial susceptibility of the bacterial pathogens isolated was determined by the Kirby-Bauer diffusion method according to the National Committee for Clinical Laboratory Standards (NCCLS). Antibiotics tested included Ampicillin 10µg, Penicillin 10µg, Chloramphenicol 30µg, Oxacillin10µg, Gentamycin

10μg, cotrimoxazole 25μg, Augumentin 10μg, Erythromycin 15 μg, Cephalothin 30 μg and Vancomycin 30μg.

After 16 to 18 hours of incubation on Muller-Hinton agar, each plate was examined. Zones were measured to the nearest whole millimetre, using sliding callipers or a ruler, which was held at the back of the inverted Petri plate. The Petri plate was held a few inches above a black, non reflecting background and illuminated with reflected light. The zone margins were taken as the area showing no obvious, visible growth that can be detected with the unaided eye. Faint growth of tiny colonies, which can be detected only with a magnifying lens at the edge of the zone of inhibited growth, was ignored. However, discrete colonies growing within a clear zone of inhibition were sub cultured, re-identified, and retested. The results were reported as sensitive, intermediate or resistant to the agents that had been tested according to NCCLS. For convenient interpretation during data analysis intermediate was categorized as sensitive.

**Quality Control**

Aseptic techniques were observed in all the steps of blood sample collection and inoculation into blood culture bottles to minimize contamination. Commercially prepared BACTEC culture vials type PEDS PLUS$^{TM}$/F (enriched soybeans-casein digest broth with $CO_2$) for aerobic cultures were used to support growth of all possible organisms causing pneumonia. The BACTEC vials were immediately placed in the BACTEC® 9050 equipment which automatically detects the positive vials to maximize the growth of organisms. All the positive vials were immediately sub cultured, gram stained and submitted for biochemical tests to avoid unnecessary delays and contaminations. All culture media were prepared according to the directions of the manufacturer. Three plates of each batch were incubated at $37^0$C for 48 hours to check for sterility and the ability to support growth of the common organisms causing pneumonia was determined by inoculating the media with a typical stock culture. Negative and positive controls were included to validate the biochemical reagents/test kits.

**FBP**: This includes haemoglobin estimation, white cell count (total and differential). One millilitres of blood was put in EDTA tube for FBP. These were determined using a cell – dyn 3500 and 3700 machines (Abbot diagnostic division, abbot laboratories, USA). A blood sample in the EDTA bottle mixed up using a mixing machine, and 1ml of blood fed into the cell – dyn machine to determine the above parameters.

**HIV:** A 5ml plain vacutainer tube for ELISA HIV testing. For children aged less than 18 months 1ml of blood was collected in a EDTA vacutainer tube for HIV - 1 DNA PCR testing.

Blood samples collected from study subjects were used for HIV testing. A preliminary HIV ELISA testing was done on all collected samples using Abbott AXSYM® system. AxSYM® HIV 1/ 2 gO is based on the Microparticle Enzyme Immunoassay (MEIA) technology utilizing recombinant HIV antigens coated on a solid phase to capture antibodies to HIV-1/HIV-2. The presence or absence of antibodies to HIV–1and/or HIV -2 in the sample is determined by comparing the rate of formation of fluorescent product to the cut-off rate which is calculated from a previous AxSYM® HIV 1/ 2 gO Index calibration. If the rate of formation of fluorescent product in the sample is greater than or equal to the cut-off rate, the sample is considered reactive for anti–HIV. Specimen that was not reactive by AxSYM® HIV 1/ 2 gO are considered negative for antibodies to HIV-1 and HIV-2. These specimen need not to be tested further. Specimens which are initially reactive are retested in duplicate. Repeat reactivity is highly predictive of the presence of HIV-1 and/or HIV-2 antibodies. For children aged 18 months or above positive AxSYM® HIV 1/ 2 gO, means the child is HIV positive.

For children aged less than 18 months samples were tested using HIV–1 DNA polymerase chain reaction (PCR) for proviral DNA. Positive HIV DNA PCR result were interpreted that the child is HIV infected and a negative result would be interpreted that the child is not HIV positive.

HIV- pre and post counselling was provided to the parents/guardian of children who were found to be HIV infected and clinical care of these children was

according to the standards of care as practiced at MNH in accordance with Ministry of Health guidelines, which includes provision of antiretroviral therapy. Counselling procedures was done by the principle investigator.

All the blood specimens for HIV testing received a code. The results were also coded. During analysis of the data these codes were used. Therefore, the names of the patients and the results were not linked.

**Blood chemistry:** One and a half millilitres of blood was put in 5mls green top Vacutainer tube for liver and renal function tests, and serum electrolytes.

**Alanine Aminotransferase (ALT)**

Amount of serum Alanine Aminotransferase (ALT) were measured using Architect c8000. The ARCHTECT system has Automatic Dilution features of which the system performs a 1:5 dilution of the specimen and automatically corrects the concentration by multiplying the results by the appropriate dilution factor.

ALT present in the sample catalyzes the transfer of the amino group from L-alanine to α-ketoglutarate forming pyruvate and L-glutamate. Pyruvate in the presence of NADH and lactate dehydrogenase (LD) is reduced to L-lactate. In this reaction NADH is oxidized to NAD. The reaction is monitored by the rate of decrease in absorbance at 340 nm due to the oxidation of NADH to NAD.

**Aspartate Aminotransferase (AST)**

Amount of serum Aspartate Aminotransferase (AST) were measured using Architect c8000. The ARCHTECT system has Automatic Dilution features of which the system performs a dilution of the specimen and automatically corrects the enzyme activity value by multiplying the results by the appropriate dilution factor.

AST present in the sample catalyzes the transfer of the amino group from L-aspartate to α-ketoglutarate forming oxaloacetate and L-glutamate. Oxaloacetate in the presence of NADH and Malate dehydrogenase (MDH) is reduced to L-malate. In this reaction NADH is oxidized to NAD. The reaction is monitored by the rate of decrease in absorbance at 340 nm due to the oxidation of NADH to NAD.

**Serum Creatinine**

Amount of serum creatinine were measured using Architect c8000. The ARCHTECT c8000 system has Automatic Dilution features.

At alkaline pH, creatinine in the sample reacts with picrate to form a creatinine-picrate complex. The rate of increase in absorbance at 500 nm due to the formation of this complex is directly proportional to the concentration of creatinine in the sample.

**Blood Urea Nitrogen (BUN)**

Amount of Blood Urea Nitrogen (BUN) were measured using Architect c8000. The ARCHTECT system has Automatic Dilution features of which the system performs a 1:5 dilution of the specimen and automatically corrects the concentration by multiplying the results by the appropriate dilution factor.

The Blood Urea Nitrogen assay is performed as a kinetic assay in which the initial rate of the reaction is linear for a limited period of time. Urea in the sample is hydrolyzed by urease to ammonia and carbon dioxide. The second reaction, catalyzed by glutamate dehydrogenase (GLD) converts ammonia and α-ketoglutarate to glutamate and water with the concurrent oxidation of reduced NADH to NAD. Two moles of NADH are oxidized for each mole of urea present. The initial rate in absorbance at 340 nm is proportionate to the urea concentration in the sample.

**Electrolytes**

The ARCHTECT c8000 System ICT (Integrated Chip Technology) is used for the quantification of sodium, potassium and chloride in serum or plasma.

Ion-selective electrodes for sodium, potassium and chloride utilize membranes selective to each of these ions. An electrical potential (voltage) is developed across the membranes between the reference and measuring electrodes in accordance with the Nernst equation. The voltage is compared to previously determined calibrator voltages and converted into ion concentration.

## 4.0 DATA MANAGEMENT AND ANALYSIS

All Case report forms /questionnaire filled were checked daily and any missing information was actively sought. Data entry and cleaning was done using EPI Info 2002 for windows program and data analysis was done using Statistical Package for the Social Sciences (SPSS) 13.0 for windows and Stata 8.0 programs.

The different causes of AE and proportion of HIV patients were determined using cross tabulation tables. Association between variables was done using the chi–squared test. A p-value of less than or equal to 0.05 was considered significant. In a table with a cell value less than five a Fisher's exact test was used for determining the association. Univariate analysis using logistic regression was done to determine individual variable contribution on the outcome of AE.

## 5.0 ETHICAL CONSIDERATIONS

Ethical clearance to conduct the study was sought from Research and Publication Committee of MUHAS. Permission to carry out the study was requested from the Executive Director MNH, Ethical department.

Parents or guardians of the children admitted were asked to consent for participation into the study after explaining the study itself, procedures and benefits of participation.

Children in the study were identified by a unique study number. Names, places of residence and hospital inpatient numbers were not included in the computerized database, and all data was handled in the strictest confidence.

All the results, blood slide for malaria, FBP, blood culture and sensitivity and CSF analysis were provided to the patient's clinician and recorded in the case records to facilitate the appropriate use of antimalarial, antibiotics and other supportive care in the management of these children. This proved to be beneficial to some children.

HIV post test counselling was provided and those children who were found to be HIV positive were referred to a comprehensive infectious disease clinic within the Department of Paediatrics and Child Health for further management and care.

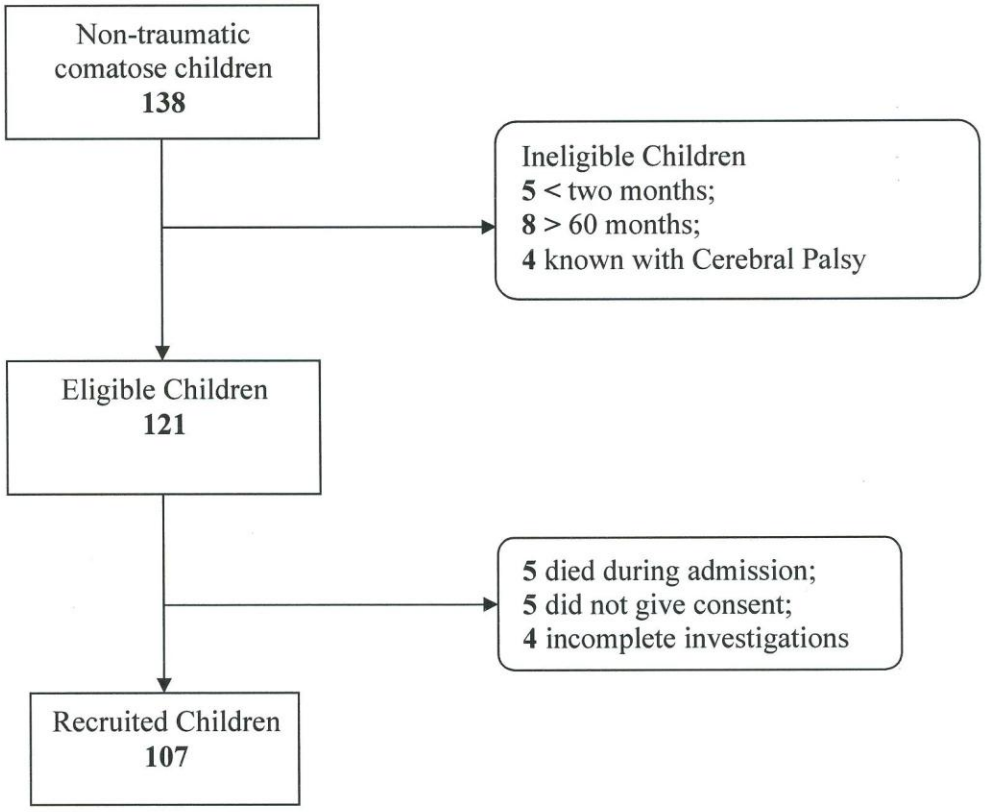
For those children who were identified to have neurological deficits, continuity of care was ensured by referral to the appropriate specialized clinic for long-term management and rehabilitation.

All study participants were treated as per the standard management protocols in paediatric wards as practiced at MNH.

## 6.0 RESULTS

This study was conducted from June 2008 to February 2009 inclusive, where 138 unconscious children admitted at Muhimbili National Hospital Paediatric wards were screened for eligibility; below is the summary of the patients flow in the study:

**Fig. 3.**




In 10 children the cause could not be classified into any of the four predetermined groups; during analysis the fifth group was formed; unclassified.

Approximately 51% of the study population were male with male to female ratio of 1.1:1.

Approximately 69% of the children were 24 months or less with age range between 2 months to 59 months, median age was 16.5 months.

In children with acute encephalopathy, 41.1% had acute bacterial meningitis, 29.8% cerebral malaria, 10.3% metabolic encephalopathy, 9.4% viral encephalopathy and 9.4% were unclassified.

**Table 1. Basic characteristics of the Study Population**

| Variables | No | % |
|---|---|---|
| **Sex** | | |
| Female | 52 | 48.6 |
| Male | 55 | 51.4 |
| **Age (Months)** | | |
| 2 -12 mon | 44 | 41.1 |
| 13 - 24 mon | 30 | 28.0 |
| 25 - 36 mon | 13 | 12.2 |
| 37 - 48 mon | 6 | 5.6 |
| 49 - 59 mon | 14 | 13.1 |
| *Median age is 16.5 months.* | | |
| ABM | 44 | 41.1 |
| CM | 32 | 29.8 |
| ME | 11 | 10.3 |
| VE | 10 | 9.4 |
| UnCl | 10 | 9.4 |

KEY: ABM – Acute bacterial meningitis; CM – Cerebral malaria; ME – Metabolic encephalopathy; VE – Viral encephalopathy; UnCl – Unclassified.

Most of the children 94 (87.9%) had a duration of coma prior to admission of 8 hours or less with median duration of 4 hours and the range of 2 – 14 hours.

History of seizures was found in 92 (86%) of the study population. Most of children 82 (76.6%) had generalised type of seizure. Other types were less common. Of those children with seizures, 15 (14.0%) had status epilepticus.

**Table 2. Clinical findings of the study population**

| Variable | No | % |
|---|---|---|
| **Duration of coma prior admission** | | |
| 0 - 4 Hours | 56 | 56.1 |
| 5 - 8 Hours | 38 | 32.7 |
| > 8 Hours | 13 | 11.2 |
| *Median duration is 4 hours* | | |
| **History of Seizures** | | |
| Yes | 92 | 86.0 |
| No | 15 | 14.0 |
| **Type of Seizures** | | |
| No seizure | 15 | 14.1 |
| Partial | 3 | 2.8 |
| Partial with secondary generalization | 7 | 6.5 |
| Generalized | 82 | 76.6 |
| **Status epilepticus** | | |
| Yes | 15 | 14.0 |
| No | 92 | 86.0 |

**Other findings:**

**Duration of illness prior admission.**

Among 107 children participated in the study, 39.3% were admitted within the first three days of the onset of the illness while 45.8% and 15% were admitted within four to six days and seven or more days respectively. Those admitted in their first three days of onset of illness 45.2% died while those admitted day seven or more had death rate of 87.5%. The chi square for trend shows a strong linear association between the duration of illness prior admission and the poor outcome, $p = 0.008$.

**Use of medication prior admission:**

Among 107 children in the study, 84 (78.5%) received treatment prior to the admission. For those who were on treatment, 55 (51.4%) of them used antimalarial while 65 (60.7%) used antibiotics. Moreover, 37 (34.6%) of them were on dual treatment, that is antimalarial and antibiotics.

From table 3; In 38% of children, the cerebrospinal fluid was turbid/cloudy.

*Haemophilus influenzae (approximately 78%)* was the most common organism identified by the microscopic examination of the CSF and was the most common organism cultured from the CSF.

Among children with positive blood culture, most of them were due to *E. coli* and *S. aureus* each accounted for (40%) compared to other organisms.

**Table 3. Laboratory findings of the study population**

| Variables | | |
|---|---|---|
| **CSF Appearance** | No | % |
| Clear | 66 | 61.7 |
| Cloudy | 12 | 11.2 |
| Turbid | 29 | 27.1 |
| **CSF Microscopy** | | |
| *E. coli* | 1 | 5.5 |
| *H. influenzae* | 14 | 77.8 |
| *S. pneumoniae* | 3 | 16.7 |
| **CSF Culture** | | |
| *H. influenzae* | 3 | 75.0 |
| *S. pneumoniae* | 1 | 25.0 |
| **Blood Cultures** | | |
| *E. coli* | 4 | 40.0 |
| Klebsiella spp. | 2 | 20.0 |
| *S. aureus* | 4 | 40.0 |

Six per cent of all children with acute encephalopathy had normal haemoglobin level, of these who were anaemic 20.0 % mild, 55.0 % moderate and 24.0 % with severe anaemia. None of the child with cerebral malaria had normal Hb while about

70.0 % had severe anaemia. Other children with ABM, ME, VE and UnCl had Hb of mild to moderate form. This difference of haemoglobin level between cerebral malaria and other aetiologies is statistically significant, $p \leq 0.001$.

Sixty percent of children had normal serum glucose level while 30% had hypoglycaemia.

Sixty percent of children with acute encephalopathy had no malaria parasite in their blood. Approximately 28% of children with bacterial meningitis had malaria parasite count less than 1000 per 200WBC compared with 68% of those with cerebral malaria. However, 100% of children with cerebral malaria had parasite count of more than 1000 per 200WBC. This difference is of statistical significant, $p \leq 0.001$.

Of 107 children admitted with acute encephalopathy, only 9 (8.4%) were HIV positive. HIV status has no association with any cause of acute encephalopathy, $p = 0.251$.

**Table 4. Characteristic distribution of causes of Acute Encephalopathy.**

| Variables | ABM | | CM | | ME | | VE | | UnCl | | Total | | p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No | % | No | % | No | % | No | % | No | % | No | % | |
| **HB Status** | | | | | | | | | | | | | |
| 11.5 -15.6 g/dl | 4 | 57.1 | 0 | 0.0 | 0 | 0.0 | 3 | 42.9 | 0 | 0.0 | 7 | 6.5 | |
| 10.0 – 11.4 g/dl | 13 | 61.9 | 1 | 4.8 | 2 | 9.5 | 5 | 23.8 | 0 | 0.0 | 21 | 19.6 | 0.000‡ |
| 7.0 – 9.9 g/dl | 24 | 43.6 | 14 | 25.5 | 7 | 12.7 | 2 | 3.6 | 8 | 14.5 | 55 | 51.4 | |
| < 7.0 g/dl | 3 | 12.5 | 17 | 70.8 | 2 | 8.3 | 0 | 0.0 | 2 | 8.3 | 24 | 22.4 | |
| **Serum glucose Status** | | | | | | | | | | | | | |
| < 3.5 mmol/l | 4 | 11.8 | 22 | 64.7 | 6 | 17.6 | 1 | 2.9 | 1 | 2.9 | 34 | 31.8 | |
| 3.5 – 7.5 mol/l | 39 | 58.2 | 9 | 13.4 | 2 | 3.0 | 8 | 11.9 | 9 | 13.4 | 67 | 62.6 | 0.000‡ |
| > 7.5 mmol/l | 1 | 16.7 | 1 | 16.7 | 3 | 50.0 | 1 | 16.7 | 0 | 0.0 | 6 | 5.6 | |
| **Malaria Parasite count** | | | | | | | | | | | | | |
| 0 | 37 | 55.2 | 0 | 0.0 | 11 | 16.4 | 9 | 13.4 | 10 | 14.9 | 67 | 62.6 | |
| < 1000 | 7 | 28.0 | 17 | 68.0 | 0 | 0.0 | 1 | 4.0 | 0 | 0.0 | 25 | 23.4 | 0.000‡ |
| > 1000 | 0 | 0.0 | 15 | 100.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 15 | 14.0 | |
| **HIV Status** | | | | | | | | | | | | | |
| Positive | 7 | 77.8 | 1 | 11.1 | 0 | 0.0 | 1 | 11.1 | 0 | 0.0 | 9 | 8.4 | |
| Negative | 37 | 37.8 | 31 | 31.6 | 11 | 11.2 | 9 | 9.2 | 10 | 10.2 | 98 | 91.6 | 0.251‡ |
| **Total** | **44** | **41.1** | **32** | **29.8** | **11** | **10.3** | **10** | **9.4** | **10** | **9.4** | **107** | **100.0** | |

**KEY**: ABM –Acute bacterial Meningitis; CM – Cerebral Malaria; ME – Metabolic Encephalopathy; VE – Viral Encephalopathy; UnCl – Unclassified.
‡p-value for Fisher's exact test

**Other findings**

Hypoglycaemia was found in31.8% of children in this study and of them 64.7% died while 73 (68.2%) were not hypoglycaemic and 58.9% of them died; the difference in mortality has no statistical significance with $p = 0.3$.

Anaemia was found in 93.5% of the study participants: in 22.4% with severe anaemia 62.5% died; 51.4% with moderate anaemia, 58.2% died and 19.6% had mild anaemia with 57.1% death. Moreover, 6.5% had no anaemia and 85.7% of them died; the difference has no statistical significance, $p = 0.5$.

Malaria parasite was found in 37.4% of the study participants. Approximately 23% of the participants had less than 1000 parasites per 200WBC and of them 48% died while 14% had more than 1000 parasites per 200WBC with 53.3% death. Moreover, of the 62.6% of those who had no malaria parasites 67.1% had died. The difference in parasite count in association with mortality had no statistical significance, $p = 0.2$.

HIV infection that was found in 9 children, 55.6% of the them were 12 months or less.

**Causes of the Encephalopathy**

Among 107 recruited children, acute bacterial meningitis was found in 44(41.12%) followed by CM 32(29.9%). Among these two major causes, ABM affect most of the children in their first 12 months of life (50%) while CM affect older children mostly above 24 months(57.6%); this difference is of statistical significance, p = 0.003. There is no significant difference of gender among various forms of acute encephalopathy, p= 0.857.

**Table 5. Distribution of causes of acute encephalopathy by age and sex**

| Variables | | ABM | | CM | | ME | | VE | | UnCl | | Total | | p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No | % | No | % | No | % | No | % | No | % | No | % | |
| **Sex** | | | | | | | | | | | | | | |
| | Male | 23 | 41.8 | 18 | 32.7 | 4 | 7.3 | 5 | 9.1 | 5 | 9.1 | 55 | 51.4 | 0.857‡ |
| | Female | 21 | 40.4 | 14 | 26.9 | 7 | 13.5 | 5 | 9.6 | 5 | 9.6 | 52 | 48.6 | |
| **Age** | | | | | | | | | | | | | | |
| | 2-12 mon | 22 | 50.0 | 6 | 13.6 | 5 | 11.4 | 4 | 9.1 | 7 | 15.9 | 44 | 41.1 | |
| | 13-24mon | 14 | 46.7 | 7 | 23.3 | 5 | 16.7 | 2 | 6.7 | 2 | 6.7 | 30 | 28.0 | 0.003‡ |
| | ≥ 25mon | 8 | 24.2 | 19 | 57.6 | 1 | 3.0 | 4 | 12.1 | 1 | 3.0 | 33 | 30.8 | |

**Outcome**

Of 107 children, only 31 (29.0%) had complete recovery at the time of discharge while 11 (10.3%) were discharged with neurological sequelae and 65(60.7%) died.

Large proportion of those who survived 42.4% were 25 months or older.

**Table 6: The outcome of acute encephalopathy by age**

| Age Group | Outcome | | | | | | | | p-value |
|---|---|---|---|---|---|---|---|---|---|
| | Recovered | | Neurologic sequelae | | Death | | Total | | |
| | No | (%) | No | (%) | No | (%) | No | (%) | |
| 2 -12 mon | 6 | (13.6) | 4 | (9.1) | 34 | (77.3) | 44 | (41.1) | |
| 12 - 24 mon | 11 | (36.7) | 3 | (10.0) | 16 | (53.3) | 30 | (28.0) | **0.029‡** |
| ≥ 25 mon | 14 | (42.4) | 4 | (12.1) | 15 | (45.5) | 33 | (30.8) | |
| **Total** | **31** | **(29.0)** | **11** | **(10.3)** | **65** | **(60.7)** | **107** | **(100.0)** | |

‡ p-value for Fisher's exact test.

**Risk factors for poor outcome**

Thirty four 34(77.3%) children who died were between 2 – 12months compared to the other age groups, and the difference was of statistical significant p=0.012. Children under 12 months had poor outcome compared to children above 24 months and the difference is statistically significant; p = 0.029.

Eighty per cent of children who were in coma for more than five hours died compared with (40%) for those with coma for less than 5 hours prior to admission, this difference is of statistical significance with a sharp contrast demonstrated, $p \leq 0.001$.

All children admitted with total Blantyre Coma Score of zero died compared to (19.2%) with coma score of three, this difference was statistically significant, $p \leq 0.001$.

All children with average Blantyre Coma Score of one died. About 79% of those with average Blantyre Coma Score of two died while all with Blantyre Coma Score of three survived, the difference was of statistical significance, $p \leq 0.001$.

Status epilepticus was highly associated with poor survival as 93.3% of them died, the difference was statistically significant $p=0.008$.

Approximately 47% of children who had no seizures died compared to 52% of those with less than four seizures who died. Moreover, 65% died with about five to eight seizures while 100% died with more than eight. So the frequency of seizures was statistically significant association with mortality, $p=0.008$.

Children with abnormal posture; decerebrate [25(96.2%)] and opisthotonus [21(75.0%)] died compared to 14(31.8%) death of Children with normal posture, the difference was of statistical significance, $p \leq 0.001$.

**Table: 7. Risk factors for mortality in children with Acute Encephalopathy.**

| Variable | Survived | | Died | | P-Value |
|---|---|---|---|---|---|
| | No | (%) | No | (%) | |
| **Age group** | | | | | |
| 2 - 12 mon | 10 | 22.7 | 34 | 77.3 | |
| 13 - 24 mon | 14 | 46.7 | 16 | 53.3 | **0.012** |
| ≥ 25 mon | 18 | 54.5 | 15 | 45.5 | |
| **Duration of Coma prior admn(Hrs)** | | | | | |
| 2 - 5 Hrs | 34 | 56.7 | 26 | 43.3 | |
| 6 - 9 Hrs | 6 | 17.1 | 29 | 82.9 | □ **0.001‡** |
| ≥ 10 Hrs | 2 | 16.7 | 10 | 83.3 | |
| **Coma score on admission (BCS)** | | | | | |
| 0 | 0 | 0.0 | 13 | 100.0 | |
| 1 | 2 | 8.0 | 23 | 92.0 | □ **0.001‡** |
| 2 | 19 | 44.2 | 24 | 55.8 | |
| 3 | 21 | 80.8 | 5 | 19.2 | |
| **Average Coma Score in the ward** | | | | | |
| 1 | 0 | 0.0 | 26 | 100.0 | |
| 2 | 7 | 20.6 | 27 | 79.4 | □ **0.001‡** |
| 3 | 35 | 100.0 | 0 | 100.0 | |
| **Status Epilepticus** | | | | | |
| Yes | 1 | 6. 7 | 14 | 93.3 | **0.004‡** |
| No | 41 | 44.6 | 51 | 55.4 | |
| **Frequency of convulsions** | | | | | |
| No convulsion | 8 | 53.3 | 7 | 46.7 | |
| 1 - 4 times | 23 | 47.9 | 25 | 52.1 | |
| 5 - 8 times | 11 | 34.4 | 21 | 65.6 | **0.006‡** |
| ≥ 9 | 0 | 0.0 | 12 | 100.0 | |
| **Posture** | | | | | |
| Normal | 30 | 68.18 | 14 | 31.82 | |
| Decerebrate | 1 | 3.85 | 25 | 96.15 | □ **0.001‡** |
| Decorticate | 4 | 44.44 | 5 | 55.56 | |
| Opisthotonus | 7 | 25.0 | 21 | 75.0 | |

‡p-value for Fisher's exact test.

**Univariate analysis of factors associated with death in children with acute encephalopathy.**

In this study, a child of 12 months or less is about 4 times more likely to die (CI 1.5 - 10.9) compared to other older children.

Children admitted with coma for 6 hours or more prior to admission were about 42 times more likely to die (CI 2.3 -17.5) compared to those who were brought in earlier (CI 0.03 - 0.76).

The Total Blantyre Coma Score was predictive of mortality as all of the children admitted with a total score of zero died; this is in sharp contrast to those with score of 3 (CI 0.002 - 0.074). Even those with score of 1 were about 13 times more likely to die (CI 2.8 - 64.9) than those with a score of 2 (CI 0.62 - 3.52).

The decerebrate and opisthotonus posture were strongly associated with mortality (CI 3.4 -205.6 and 1.9-14.9 respectively) compared with the normal posture (OR 0.2, CI 0.08 - 0.51). The decorticate posture was not strongly associated with mortality (CI 0.33 - 5.32) in this study.

The status epilepticus was strongly associated with mortality (CI 1.31 - 83.9).

In this study children who had duration of illness prior to admission of less than four days (CI 0.15 – 0.77) were more likely to survive while those whose duration of illness prior admission was more than six days were strongly associated with mortality (CI 1.15 – 24.95).

**Table 8: Predictors of death in children with acute encephalopathy**

**Univariate logistic regression of selected variables associated with death**

| Variables | N | % | N | % | OR | 95% CI | p-value |
|---|---|---|---|---|---|---|---|
| **Age group** | | | | | | | |
| ≤ 12 mon | 34 | 77.27 | 44 | 41.12 | 4.08 | 1.51 - 10.91 | 0.005 |
| 13-24 mon | 16 | 53.33 | 30 | 28.04 | 1.37 | 0.51 - 3.70 | 0.533 |
| 25-36 mon | 5 | 38.46 | 13 | 12.15 | 0.58 | 0.17 - 2.01 | 0.387 |
| 38-59 mon | 10 | 50.0 | 10 | 18.69 | 1.05 | 0.36 - 3.03 | 0.932 |
| **Duration of Coma Prior Admission** | | | | | | | |
| 2-5 Hours | 26 | 43.33 | 60 | 56.07 | 0.15 | 0.03 - 0.76 | 0.022 |
| 6-9 Hours | 29 | 82.86 | 35 | 32.71 | 6.32 | 2.29 -17.47 | 0.000 |
| ≥ 10 Hours | 10 | 83.33 | 12 | 11.21 | 6.54 | 1.32 - 32.44 | 0.022 |
| **Coma Score on Admission (TBCS)** | | | | | | | |
| 0 | 13 | 100.0 | 13 | 12.15 | | | 0.000 |
| 1 | 23 | 92.0 | 25 | 23.36 | 13.42 | 2.77 - 64.88 | 0.001 |
| 2 | 24 | 55.81 | 43 | 40.19 | 1.47 | 0.62 - 3.52 | 0.383 |
| 3 | 5 | 19.23 | 26 | 24.3 | 0.01 | 0.002 - 0.074 | 0.000 |
| **Posture** | | | | | | | |
| Normal | 14 | 31.82 | 44 | 41.12 | 0.20 | 0.08 - 0.51 | 0.001 |
| Decerebrate | 25 | 96.15 | 26 | 24.3 | 26.43 | 3.40 - 205.60 | 0.002 |
| Decorticate | 5 | 55.56 | 9 | 8.41 | 1.32 | 0.33 - 5.32 | 0.695 |
| Opisthotonus | 21 | 75.0 | 28 | 26.17 | 5.37 | 1.93 - 14.93 | 0.001 |
| **Status Epilepticus** | | | | | | | |
| | 14 | 93.33 | 15 | 16.3 | 10.5 | 1.31 - 83.9 | 0.027 |

Where OR denotes Odds ratio, CI confidence interval and N row total.

## 7.0 DISCUSSION

Acute Bacterial Meningitis and Cerebral Malaria were the major cause of morbidity (41.1% and 29.9% respectively) in this study, others (Metabolic Encephalopathy and Viral Encephalopathy) contributed to approximately (10%) each. This reiterates that bacterial infections are still the commonest cause of morbidity and mortality. The smaller proportion of malaria may be caused by the campaign to reduce the burden of malaria, including the use of insecticide treated nets, pesticide control, judicious use of antimalarial and environmental sanitation. [50] In contrast, there is relatively little to prevent ABM. Our findings indicate that meningitis is an important cause of encephalopathy. Malaria may have been over diagnosed in this setting, and it is frequently possible to find co-infection of malaria and bacterial meningitis. In this study, those who had malaria parasitaemia and proven bacterial meningitis have been categorised as bacterial meningitis, although treated for both conditions, since bacterial meningitis was considered as more lethal of the two. Over diagnosis of malaria is reported in several countries, as indicated in a study done in Kenya. [51]

*Haemophilus influenza* was the commonest organism isolated in this study. This is expected as it is the common causative agent of meningitis in children less than five years, in this case most of children affected were below 24 months. *Haemophilus influenzae* is a capsulated organism and children at this age are more susceptible as they cannot mount immune response enough to combat these agent. These results are similar to other studies in Kenya and Eritrea.[2,17-20] This infection is preventable by vaccine,[17,20,52] and many African countries have incorporated the use of Hib vaccine in their schedules. This effective vaccine against *Haemophilus influenza* type b has just been introduced in the EPI program in Tanzania as of April 2009, and is administered along with DPT-HB as a pentavalent vaccine. We expect that in few years to come that *Haemophilus influenzae* will be less isolated as a cause of meningitis.

About 60% and 49% of children used antibiotics and antimalarial drugs respectively prior to admission in this study. This is due in part to the common

practice in Dar-es-Salaam to give medication to any child with febrile illness without proper investigations. Usage of antibiotics and anti-malarial create a separate category of scenario, whereby, there is an element of partial treatment, and often masking of the aetiology as evidenced in our findings. In a study done previously in Muhimbili National Hospital, [53] 91% of patients seen at the facility had received some form of antimalarial drug at home, or by a pharmacists, or health centre. Similar reports are available from Malawi [4] and Nigeria [54] where 50% and 69% had antimalarial drugs prior admission respectively; however in these studies they had a wider age range though the age range of my study participant was covered.

Severe anaemia in combination with other factors such as hypoglycaemia especially in children with cerebral malaria is one of the determinants of poor prognosis.[49,55] However, in the current study neither anaemia nor hypoglycaemia has association with poor outcome. Nevertheless severe anaemia was significantly associated with cerebral malaria compared to other aetiologies. This could be due to the fact that malaria parasitaemia is associated with increased red cell haemolysis. Severe anaemia in our environment may also be due to various factors, including poor nutrition, worm infestation, and recurrent infections. Therefore, since anaemia cuts-across all conditions, it is not particularly related to differences between the encephalitis, but may be underlying factor for general increase morbidity. Other studies have also showed no association between anaemia and mortality.[4] Moreover, because of triaging and observing emergency signs, children with severe anaemia receive blood transfusion urgently and thus the mortality is averted.

Likewise, hypoglycaemia was marked in children with cerebral malaria compare with other aetiologies. Although hypoglycaemia is expected to be equally present in children who are severely sick due to poor food intake. The most likely explanation to why hypoglycaemia is significantly observed in children with cerebral malaria may be due to multiple organs failure including the liver which is important in metabolism of glucose. The presence of hypoglycaemia on admission was also not related to outcomes, for similar reasons as for severe anaemia, and that is,

immediate resuscitation and correction of hypoglycaemia was pursued. A study done on specificity of hypoglycaemia and cerebral malaria in children found no specific association between hypoglycaemia and cerebral malaria. [56]

About 60% of children in this study died. This may be due to the fact that these are very sick children, who were not investigated properly and appropriate treatment was not promptly provided at their first contact with health facility. However, if these children would have been investigated thoroughly and proper treatment given at the point when they were first seen, the mortality would have been much lower. These findings are relatively higher than in others studies where the mortality rate ranges from 10% to 50%. [15, 17, 26, 34] Study done at Muhimbili [53] on children with of the same age group that have cerebral malaria had mortality of 30%. This observation can be explained by the fact that most of these children with poor outcome had longer duration of illness prior admission: those with three days or less had 45.2% mortality compared to 65.3% death in those with four to six days. Moreover, 87.5% died among those with more than six days of illness prior admission. Also the use of antimalarial and antibiotics prior CSF examination that in part impairs the isolation of the infective microorganisms and hence proper treatment according to the aetiology and sensitivity pattern. Moreover the lack of nursing staff in the municipal hospitals may also contribute to this picture as monitoring of these children is of paramount importance.

In children who survived, 10.3% were discharged with neurological sequelae. As these children had CNS infection, various degree of damage is expected depending on the severity and other manifestations such as multiple convulsions these children had that may cause brain damage due to hypoxia. These findings are similar with other studies where the prevalence of neurological sequelae was found to be about 10.9%.[34] In the study that was previously done at Muhimbili [53] on children with cerebral malaria 11% were discharged with neurological sequelae.

Young children have poorly developed immune system of which with time it is built up. This makes them prone to severe infections, and when they get infection if not properly managed it carries a poor prognosis. Children with age of 24 months

or less had a poor outcome compared to the older age group; this was significantly contributed by those children less than 12 months in the current study. Since infections in these children tend to be overwhelming causing multiple organ failure that ultimately contributes to the poor out come. This is similar to study done in Malawi that showed poor prognosis was associated with age less than three years. [4] However, this is in contrast with the study done at Muhimbili in 1995 that showed no association between age and outcome. [53]

A Blantyre Coma score of zero on admission was strongly associated with mortality compared with coma score above zero. The average coma score of one or less was strongly associated with mortality. This can be explained by the fact that, the more the brain injury the lower the coma scores. This has a bearing on the outcome as it is difficult for the child with severe brain injury to survive and if they do then will be with neurological sequelae. These findings are consistent with those found in Malawi.[4] However this is in contrast with study done at Muhimbili where there were no significant difference between coma score of zero and above zero in predicting the outcome. Although in the study done at Muhimbili enrolled only those with coma score of two to zero while in this study is from three to zero, however, even in this study there is significant difference between children with coma score of two and zero in association with mortality. This may be explained by larger sample size in this study compared to the previous Muhimbili study. [53]

Children recover differently from CNS infection. This is mostly determined by the severity of the infection, the site mostly affected the relative maturity of CNS of that particular child, the aetiology and complications like frequent convulsions. So, most of children with severe CNS infection tend to present with various abnormal posture depending on the part of the brain affected. Children with severe CNS infection mostly present with decerebrate, decorticate or opisthotonus posture. As these postures signify severe brain damage, a poor outcome is expected in a child presenting with them. This study showed significant association between posture and poor outcome. This is similar with other studies done in Malawi[4] and Kenya,[29] however decorticate posture had no significant association with poor outcome and

this is in contrast to these other studies. This may be explained by the smaller number of patients who had decorticated posture in the current study. In a previous study done at Muhimbili, decorticate posture was also associated with poor outcome. [53]

Children with acute encephalopathy have a tendency to have seizures. These convulsions are usually differing in characteristics such as frequency, duration and type. Regardless of the type most of them usually are short lived, but when severe and of longer duration for more than 30 minutes they are called status epilepticus. However even when convulsion last for more than ten minutes it is managed as if it were status epilepticus, since it has been shown that when a child have convulsion for more than five minutes, it may cause brain damage.[57,58,59] The chance of severe brain damage increases as the frequency of convulsions as this predisposes the brain to multiple insults. In this study the frequency of convulsions had a significant association with poor outcome. These findings are similar to a study on risk factors for persisting neurological and cognitive imparements following cerebral malaria that was done in Kenya.[26]

Status epilepticus is a life threatening paediatric emergency that results from an inability to normally abort an isolated seizure either due to ineffective inhibition, or due to abnormally persistent excessive excitation. This usually leads to severe brain hypoxia with resulting severe brain damage with a poor outcome. In this study children with status epilepticus had a significant high mortality. This may be due to the fact that most of these events started at home where the proper care was not available and the logistics of taking these children to hospital cost more time and thus children arrive at hospital with severely affected CNS. These findings are similar with studies done in Kenya on neurological outcomes in children with cerebral malaria. [2, 26]

Human immunodeficiency virus is common in children born from HIV positive mothers. The burden of HIV in sub-Saharan Africa paediatric population cannot be over-emphasised. HIV infection is one of the causes of encephalopathy in children and also due to its immunosuppressive effect it can easily predispose a child to

other severe CNS infections. In this study 8.4% of children were HIV positive and none of them were on ARV drugs. This is significantly higher than the prevalence in the general paediatric population in Tanzania which is less than two percent. However, a study done at Muhimbili [60] in 1991 showed much higher prevalence of 21% in all admissions. This may be explained by the fact that the current study and that of 1991 are hospital based studies involving very sick children compared to a community based study that shows significantly low prevalence. However, in the current study there were no association between HIV status and the outcome of these children.

## 8.0 LIMITATION OF THE STUDY

1. Autopsy was not done due to socio-cultural reasons; this could have been of help to determine the cause of death.
2. Children less than eight months were assessed using the same parameters as older ones in Blantyre coma scoring. It was possible to use other method specific for those under eight months but it would have been not accepted to make a conclusion that kind of result.
3. Cerebro-spinal fluid processing delays at the main laboratory reception may have lead to decrease in the yield of microorganisms due to lysis of cells in the CSF. This is rather a system problem as per current SOP's does not give required priority to the CSF specimen processing. However, at times the attending receptionist at their own discretion were kind enough to waive the delaying protocols on CSF specimen.

## CONCLUSION

Acute encephalopathy are associated with high mortality rate 60.7% and 10% have neurological deficit.

Acute bacterial meningitis particularly H. influenzae is the most common in children less than two years whilst cerebral malaria is the most common in children above two years.

The risk factors for poor outcome were age under one year, longer duration of illness prior admission, longer duration of coma prior admission, total Blantyre Coma Score of zero on admission, average coma score of below two while in the ward, frequent convulsions, status epilepticus and abnormal posture.

The prevalence of HIV was found to be 8.4% and of these, 55% were children less than 12 months.

## *10.0 RECOMMENDATIONS*

*With high mortality* rate in this study; a larger study should be done to address factors both at community and health care facility level to speed up presentation and early treatment of children with acute encephalopathy.

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