CHILDHOOD BACTERIAL MENINGITIS: ANTIMICROBIAL USE PATTERN AND TREATMENT OUTCOMES IN JIMMA UNIVERSITY SPECIALIZED HOSPITAL, SOUTHWEST ETHIOPIA

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Abstract

Background: Bacterial meningitis continues to be an important source of mortality and morbidity in infants and children throughout the world despite advances in antibiotics; the major burden being in the developing countries.

Objective: To assess antimicrobial use pattern and determine treatment outcomes among children hospitalized with bacterial meningitis.

Methods: Hospital based prospective observational study was conducted among infants and children admitted to pediatric ward of Jimma University Specialized Hospital from February 25 to April 29 2015. The data was collected with pretested questionnaire and entered into Epi Data version 3.1, then exported to SPSS version 20.0 for analysis. Univariate analysis was done for all independent variables and variables with $p < 0.25$ were selected to fit multivariate logistic regression. Finally, multivariate logistic regression was performed to determine independent predictors of poor outcomes. An odds ratio and 95% confidence interval was used and the level of statistical significance was considered at $p < 0.05$.

Results: Data was analyzed for a total of 89 patients treated for bacterial meningitis. The most frequently used initially antibiotic regimen in young infants was Ampicillin plus Gentamycin (86.8%); while the majority (66.7%) of patients in older infants and children initially managed with Crystalline penicillin plus Chloramphenicol. Among the treated patients, 67.4% improved without acute complication, while the remaining 32.6% had poor outcomes (9% died, 18% had delayed fever and 5.6% had acute neurologic complications). Antibiotic change from empiric therapy was independent predictor of poor outcomes in young infants (AOR= 4.42, 95% CI (1.01-19.44**)**). However for older infants and children: irritability (AOR=38.39, 95% CI (1.78-829.36)) and seizure prior to admission (AOR=27.53, 95% CI (1.45-522.35)), initial antibiotic regimen with ceftriaxone plus gentamycin (AOR=66.48, 95% CI (3.16-1400.13)), and missed doses of antibiotics (AOR=47.33, 95% CI (2.14-1046.19)) independent predictors of poor outcomes.

Conclusion: The use of antimicrobials in this study was almost in line with the recommendation and at discharge nearly one-fourth of the patients treated for bacterial meningitis experienced poor outcomes implicating still the need for more attention during treatment.

Key words: Childhood, bacterial meningitis, antimicrobials, poor outcomes, Ethiopia

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Acronyms and abbreviations

ABs/AMs- Antibiotics /Antimicrobials

BBB – Blood Brain Barrier

BM- Bacterial Meningitis

CI- 95% Confidence Interval

CNS – Central Nerves System

CSF – Cerebrospinal Fluid

FMHACA- Food, Medicine and Healthcare Administration and Quality Control Authority

FMOH- Federal Ministry of Health of Ethiopia

GBS – *Group B Streptococcus*

HIb – *Haemophilus Influenzae Type b*

HIV- Human Immunodeficiency Virus

IQR- Interquartile Range

JUSH - Jimma University Specialized Hospital

LBW – Low Birth Weight

NBW – Normal Birth Weight

NICU – Neonatal Intensive Care Unit

OR- Odds Ratio

SAM- Sever Acute Malnutrition

UTI- Urinary Tract Infection

VLBW – Very Low Birth Weight

WHO- World Health Organization

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1. INTRODUCTION

1.1. Background

Meningitis is one of the most common types of central nervous system (CNS) infection. It is an inflammation of the meninges; that involves the subarachnoid space or spinal fluid (1). Even though there are a number of causes of meningitis (like bacterial, viral and fungal), bacterial meningitis is one of the most potentially serious infections occurring in infants and older children (2). This might be due to the acute nature of bacterial causes and the immature immunity of these age groups. Acute bacterial meningitis (BM) is associated with a high rate of acute complications, mortality and risk of long-term morbidity despite the use of advanced antibiotic therapy (3).

The causes of bacterial meningitis vary with ages in pediatrics. The most common bacterial causes of neonatal meningitis are *group B streptococcus (GBS), Escherichia coli (E. coli)* and *Listeria monocytogenes (LM)* (1); that are mainly acquired from the maternal birth canal during delivery. Whereas, the commonest etiologic agents in children beyond the neonatal period are: *Haemophilus Influenzae Type b (HIb), Neisseria meningitides* and *Streptococcus pneumoniae* (4). However, these are not the only organisms limited to pediatrics; alterations of host defense due to anatomic defects or immune deficits also increase the risk of meningitis from less common pathogens such as *Pseudomonas aeruginosa* and *Staphylococcus aureus* (1).

The Clinical features are almost similar regardless of etiologic agents. In neonates initially, non-specific features, including fever or hypothermia, failure to feed, vomiting, and later lethargy, seizure, and full fontanel but meningeal signs are generally rare (1). In infants whose cranial sutures are still open; fever, vomiting, irritability, lethargy, convulsion, and bulging of the anterior fontanel are common. However, in older children headache and focal neurologic signs like sixth nerve palsy or signs of meningeal irritation (such as nuchal rigidity, kerning's sign or Brudziniski sign) are usually present (4).

Though the definitive diagnosis of meningitis requires the analysis of spinal fluid chemistry and identification of specific pathogens from culture of the CSF (5); in most resource limited facilities the diagnosis mainly relies on clinical features and some CSF analysis (stain, WBC count, proteins and glucose measurement).

Appropriate empiric antimicrobial treatment should be initiated as soon as possible after the diagnosis is considered to reduce the risk of mortality and complications due to delay in treatment(6). The choice of empiric antibiotics should take into consideration blood brain barrier (BBB) penetration, the local epidemiology, early versus late disease, resistance patterns and availability within resource constraints (7).

In resource limited settings the treatment of pediatric bacterial meningitis generally has two protocols based on age (under 2 months and above 2 months of age) (3,4,7). Accordingly, for neonates and young infants (under 2 months of age) the first-line antibiotics are Ampicillin and Gentamicin and alternatively, a third-generation cephalosporin, such as Ceftriaxone(8) or Cefotaxime plus Gentamycin (5). For infants and children (above 2 months of age) the first line is the combination of Penicillin G and Chloramphenicol and the alternative is Ceftriaxone (8), or Cefotaxime(4). For patients not responding to the first line regimens, vancomycin plus ceftazidime can be considered (2,8,9).

Table 1 Doses, frequencies and durations of empirical antimicrobial regimen for treatment of childhood bacterial meningitis, by age ([a, e]) (2,8,9)

Antimicrobials	**0-7 days**	**8–28 Days**	**Infants and Children**
Ampicillin	200–300 divided q8h	300 divided q4h or q6h	300 divided q4–6h
Cefotaxime	100 divided q12h	150–200 divided q8h or q6h	200–300 divided q8h or q6h
Ceftriaxone([d])	—	—	100 divided q12h or q24h
Ceftazidime	150 divided q12h	150 divided q8h	150 divided q8h
Chloramphenicol	—	—	100mg/kg/day IV q6h
Gentamicin([b, c])	5 divided q12h	7.5 divided q8h	7.5 divided q8h
Penicillin G	250,000–450,000 divided q8h	450,000 divided q6h	450,000 divided q4h or q6h
Vancomycin([b, c])	30 divided q12h	30–45 divided q8h	60 divided q6h

a. Dosages in mg/kg (U/kg for penicillin G) per day.
b. Smaller doses and longer dosing intervals, for very low birthweight neonates, may be advisable
c. Monitoring of serum levels is recommended to ensure safe and therapeutic values
d. Use in neonates is not recommended because of inadequate experience in neonatal meningitis.
e. Duration of treatment 14-21days for infants under 2 months (gentamycin only for 2 weeks), 10-14 days for infants and children above the age of 2 months (5).

Adjuvant steroids have some benefits in certain cases of BM (pneumococcal and H. influenza) by reducing inflammation and improving outcome. The recommended dose of dexamethasone in bacterial meningitis is 0.15 mg/kg, every 6 hours for 2–4 days. It should be given within 10–20 min before or during administration of antibiotics(5). There is insufficient data to recommend steroids in ages < 6 weeks (4, 8).

1.2 Statement of the problem

Bacterial meningitis is a severe, potentially life threatening infection that is associated with high rates of mortality, morbidity and significant disability in survivors(12). The mortality of untreated bacterial meningitis approaches 100% (3), and despite the availability of newer antibiotics and preventive strategies, these morbidity and mortality due to bacterial meningitis has continued in the past two decades (3,12).

Globally, bacterial meningitis affects approximately 1.2 million people each year, with more than two thirds of these occurring before 5 years of age(14). It causes almost 170,000 deaths (14%)(15) and as many as 50 % of survivors experience neurological sequelae(16). In recent years, overall mortality rates related to bacterial meningitis of around 20% to 25% have been reported by major centers (15). WHO reported bacterial meningitis as an important cause of childhood morbidity and mortality apart from the five major killer diseases of children under five years (acute respiratory infections - mostly pneumonia, diarrhoea, measles, malaria and malnutrition)(17).

African children have the highest incidence rates of bacterial meningitis in the world(18). The consequences of bacterial meningitis in Africa is also associated with high cases fatality and frequent neuropsychological sequelae(19). The three leading causes of bacterial meningitis (Pneumococcal, Meningococcal, HIb) are vaccine preventable, however non-implementation of vaccines in Africa as well as other resource limited settings highly contributed to these disproportionate burden (20).

Even though childhood deaths reportedly decreased in the last century because of medical intervention, Ethiopia is still one of the six countries in the world where half of childhood deaths occur (21). The majority of causes being infectious diseases like meningitis. Bacterial meningitis alone accounts for about 6-8% of all causes of the hospital admissions in Ethiopia and the case fatality rates associated with bacterial meningitis is as high as 22-28%. It has remained a serious health concern for Ethiopia too for the past few decades(11,22). Recently (2007), from the Gilgel Gibe Field Research Center, meningitis was reported as the 4th top cause of death for infants older than 28 days and children only following pneumonia, malaria, diarrheal diseases (23).

The consequences of all these lead to a considerable emotional, financial and human resources burden on the family as well as the health care system (24).

In general, the occurrence of adverse consequences of bacterial meningitis in developed countries is strongly reduced by vaccination strategies, advances in antibiotic treatment, and good care facilities. In contrast, those resource limited countries are exposed to a number of factors that lead them to be vulnerable to those consequences of bacterial meningitis. To mention some: (a) Non-implementation of vaccination programs against major meningeal pathogens; (b) Late presentation of patients, having been given antibiotics without a definite diagnosis in primary or private settings, consequently, many CSF samples do not show the causative agent; (c) Late and insufficient CSF culture and Gram-staining results even though they are basic for definitive diagnosis and guiding treatment; (d) Many hospitals cannot afford expensive third generation cephalosporins and rely on chloramphenicol and penicillin as the first-line antibiotic treatment for meningitis; and (e) Intensive care units are few and not always well staffed (25).

Thus, the aim of this study is to assess the commonly used of antimicrobials in childhood BM and determine predictors for poor outcomes.

2. LITERATURES

2.1. Literature review

Despite advances in antibiotics, childhood BM continues to be an important source of substantial mortality and morbidity throughout the world (3). It causes almost 170,000 deaths each year (15) and as many as 50 % of survivors experience neurological sequelae(16). Age wise distribution of the diseases and it burden are higher in infants than older children, the highest being in neonates (14,23). Considering its regional distribution, neonatal mortality from BM in developing countries is estimated to be 40–58%, versus 10% in developed countries (7).

A number of studies have been done in different parts of the world to determine different alarming signs of the adverse consequences of childhood BM (13,23-30,40-50). Majority of the studies were from the developed countries while the burden resides in the developing ones. Characterization of these factors is important so as to take effective measures to alleviate the problems. Most of these studies focused on etiologic pattern (12,26-29) clinical features (12,23,25-27,30-40) and laboratory findings(25,27, 34, 37,40-44), however only few studies on comorbidities of BM (33)(38) and antimicrobial regimen used to treat BM (23,27,39,46-49).

a) Baseline characteristics of patients with BM

Many clinical features prior or at hospital admission are associated with the outcome of BM (12,23,25-27,30-40). Identification of the risk factors for poor outcome at hospital admission and characterization of those risk factors that develop during the course of illness would give valuable information for the health care team attempting to keep a balance between the patient's needs and existing resources.

A retrospective study conducted in Greek highlighted some risk factors for sequelae due to childhood BM. These were: bulging fontannel (RR=2.80, 95% CI (1.52-5.15)), poor feeding (RR=1.92, 95% CI (1.16-3.17)), seizure on admission (RR= 4.61,95% CI (2.88-7.38)) and duration of symptoms (>24 hours) prior admission (OR= 2.1 95% CI (1.2-3.8))(27). Similarly, another study conducted in sub-Saharan Africa reported that, longer duration of symptoms (>3 days) at presentation was significantly associated with sever neurological sequelae (OR= 3.73(1.24-11.26)) (12). However, the study from Uganda showed even delayed presentation after 6.5 days of symptoms did not appear to be an important factor for overall mortality. There was

no significant difference between the two outcome groups in the duration of symptoms (> 6.53 days) before presentation (difference in 2 groups=0.025, p=0.87) (42). Similarly, a study from Prishtina also showed that duration of > 48 hours illness before admission (42%, p= 0.59) failed to show statistically significant associated with increased risk of neurological complications (43).

Impaired consciousness prior admission was also found to be significantly associated with both death (OR= 2.61(1.17-5.03)) and sever neurological sequelae (OR= 2.96(1.32-6.63)) according to the study from sub-Saharan Africa. In the same study, seizure before admission was found to be an independent predictor of both death (OR= 2.49(1.36-4.58)) and sever neurological sequelae (OR= 9.34(3.49-25.00)). Though sever dyspnea did not independently predict sever neurological sequelae (OR= 1.44, 95% CI (0.05-4.12)), it significantly increased the risk of death (OR=2.42, 95% CI (1.17-5.03))(39). Similarly, Antoniuk SA et al (12) clearly put that clinical features of severity characterized by impaired consciousness (OR= 7.0, 955 CI (1.3-36.5))and seizures on admission (OR= 33.4, 95% CI (3.6-310.3)) were found to be strong predictors of acute neurologic complications.

Furthermore, according to Namani S et al (43), predictors identified to the increased risk of neurological complications were: age younger than 12 months (61%, p=0.00009), altered mental status (82%, p= 0.0001), and seizures prior to admission (36%, p= 0.0003).

To date, there has been lack of studies to examine the effects of specific comorbidities on bacterial outcomes. Instead some studies crudely reported comorbidity like ‘the prevalence of neonatal meningitis in suspected sepsis was 17.9%’ (38). Similarly in one study presence of comorbidity (23%, p=0.69) failed to show its statistically significant association with increased risk of neurological complications (43).

Additionally, different studies identified the following risk factors for poor outcomes of BM (mainly of death and neurological complications): seizure on/prior admission (42,43), impaired consciousness or coma at presentation (38), delayed presentation (39), and being infant(14,34).

b) Treatment outcomes of childhood BM

Early initiation of an optimal antibiotic therapy for confirmed or suspected BM, pending the CSF results, has been shown to be one of the most important factor to reduce morbidity and lethality

(4,5,9,10,54-57). The median time to treatment initiation according to study from Italy was 1 hour (48), whereas it was 9.6 hours from Uganda (42).

Improvements in outcomes of BM have been seen in developed countries, due to some advances especially in health facilities, supportive care, effective vaccination strategy, development of intensive care units, and availability of highly effective antibiotics and use of better diagnostic aids; however, in developing countries the burden continued (25). In 2010 Best and Hughes in their clinical review of evidence behind the WHO guidelines; reported mortality due to childhood meningitis in the developed world found to be 5%, compared to approximately 30% in the developing world (49). In neonates however the mortality due to meningitis was still high (almost 2 fold), in developing countries it is estimated to be 40–58%, versus 10% in developed countries (7).

In Africa these figures were reported to be much higher. For example; a study from Angola during 2004 showed that the in-ward fatality rate was 33% and severe neurological sequelae developed in 25% patients among the survivors (39). However, more adverse outcomes were reported from Uganda's study; mortality of 36.8%, sequelae (28.9%) and only 19.7% of patients improved without sequelae. The possible explanations raised by the authors of Uganda's study were: relatively high frequency of H. influenzae and other gram-negative organisms, and recently reported antimicrobial resistance to penicillin/chloramphenicol showing the need for reviewing of the existing recommendations for initial therapy in this region (42). Similar results were reported from prospective study in Prishtina (Kosovo). Among the children treated for BM 43% developed neurological complications (43).

In contrast to the above, a study of Sudanese under 5 years children reported lower incidences in both case fatality rate of 5.15% and neurological complications of 12.37%. Better awareness and advances in investigations that were not available in Sudan previously were the possible reasons raised by the author for the improvement (50).

There have been few studies found to compare different AB regimens with their outcomes of BM. The study in Greek being one among such studies, showed that penicillin had a protective effect on the occurrence of ventriculitis (OR= 0.17, 95% CI (0.05–0.60)), while treatment with chloramphenicol had an elevated risk of ventriculitis (OR= 17.77 95% CI (4.36–72.41)) and seizure disorder (OR= 4.72, 95% CI (1.12–19.96)). Cephalosporins were related to an increased

risk of hydrocephalus (OR= 5.24, 95% CI (1.05–26.29)) and ventriculitis (OR= 5.72, 95% CI (1.27–25.76)) (41). A similar result was reported from the study conducted in Sub-Saharan Africa comparing antibiotic treatment with ceftriaxone and that of penicillin plus chloramphenicol in childhood BM. The finding showed that treatment with ceftriaxone, instead of the primary regimen with penicillin plus chloramphenicol, did not improve the prognosis as the mortality rate among patients who received ceftriaxone (17/59) versus penicillin plus chloramphenicol (77/266) was similar (29%, p>0.99) and severe neurological sequelae developed in both groups were almost comparable 24% (10/ 41) for ceftriaxone versus 25% (48/190) for penicillin plus chloramphenicol (p>0.99) (39).

Steroids have some benefit in certain cases of bacterial meningitis (H. Influenza, Tuberculous and pneumococcal) by attenuating host's inflammatory response and improving outcome (5). Most current recommendations for the use of dexamethasone in infants and children is to considered for those older than 6 weeks, after weighing the potential benefits and possible risks (7,9). This excludes neonates and infants younger than 6 weeks since data are lacking to support the use dexamethasone as adjuvant therapy in this age (5). In some studies the protective effect of dexamethasone failed to show statistical significance, OR= 0.82, 95% CI (0.18–3.79) (41), in other its use failed to show increased risks of adverse outcomes (RR=1.01, 95% CI (0.58-1.77))(42), however its use was even associated with increased risk of neurological complications (97%, p= 0.01)(43).

The duration of treatment depends basically on causative agents; however in the absence of confirmatory tests it relies on the patients' condition and sometimes the age of patient is taken in to account to suspect the causative agents, thereby duration. Some guidelines for developing countries recommend 14-21 days treatment for young infants and 10 days for children older than 2 months (3,4,8). Therefore, the hospital stay can be different for different age groups or status of the patients during treatment. One study showed that the median hospital stay was significantly different; 18 days (1-40 days) patients with complications and 9 days (3-14 days) among the children without complications (p < 0.001) (12).

2.2 Significance of the study

Despite majority of the burden due to childhood bacterial meningitis occurring in the developing world, the most currently existing literature originated from wealthy countries. To our knowledge, limited studies have been done in our country regarding prevalence (22,46), etiology (11,47), diagnosis (11), antimicrobial sensitivity (51), and outcomes of meningitis (52), however studies concerning treatment and its outcomes were lacking. Therefore, the need of further study in our set up was unquestionable to assess antimicrobial use pattern and determine predictors of poor outcomes of childhood BM.

The information generated by this study is primarily important for the hospital to review its management protocol. It can also provide additional input for policy makers to support decision making that improve the functioning of the health care systems in the country. Furthermore, it can also be used as a source for teaching and training purposes, and serve as baseline for further studies.

2.3 Conceptual framework

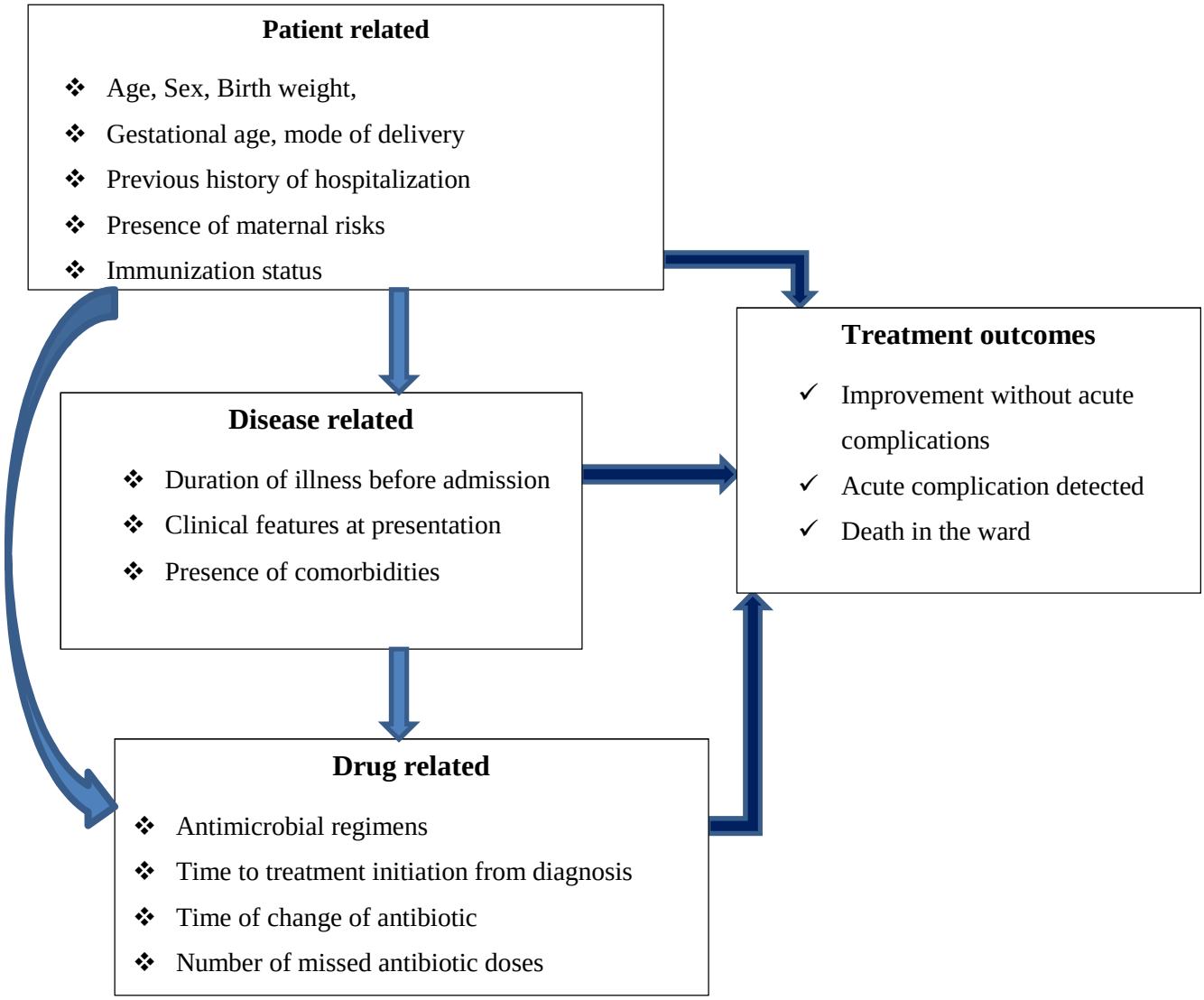

Figure 1 Conceptual framework of predictors for outcomes of children treated for BM in JUSH

3. OBJECTIVES

3.1 General objective

- To assess antimicrobials use pattern and determine treatment outcomes in children hospitalized with BM in pediatric ward of JUSH, Southwest Ethiopia, from February 25 to April 29 2015.

3.2 Specific objectives

1) To identify commonly used antimicrobials for childhood BM
2) To determine the short term treatment outcomes of childhood BM
3) To determine predictors for poor outcomes of childhood BM

4. METHODS AND MATERIALS

4.1 Study area and period

This study was conducted in the pediatric ward of JUSH. JUSH is found in Jimma Town which is located 335 Km Southwest of Addis Ababa, the capital of Ethiopia. Currently JUSH is the only teaching and referral hospital in the southwestern part of the country. It has 450 beds and more than 750 staff of both supportive and professional. It provides services for approximately 9,000 inpatient and 80,000 outpatient attendances per year coming to the hospital from the catchment population of about 15 million people as well as the neighboring regions like Gambela and some parts of Southern nation nationalities and people regional state. The hospital delivers health services in many specialty areas. These include Pediatrics and Child health, Gynecology and Obstetrics, Surgery, Internal medicine, Ophthalmology, Psychiatry, and Dentistry. The pediatric department has 101 beds with a perceived more than 100% occupancy rate and has two units; Neonatal Intensive Care Unit (NICU) and general pediatrics. Currently the ward is run by 1 subspecialist, about 9 specialists, 16 residents and 49 nurses (53). The study period was from February 25 to April 29 2015.

4.2 Study Design

Hospital based prospective observational study

4.3 Population

4.3.1 Source population

All pediatrics admitted to pediatric ward of JUSH with a diagnosis of BM

4.3.2 Study population

All pediatrics admitted to pediatric ward of JUSH with a diagnosis of BM during the study period and fulfilled illegibility criteria.

4.3.3 Inclusion and Exclusion criteria

4.3.3.1 Inclusion criteria

All pediatrics cases which were clinically suspected or confirmed as meningitis and started treatment for BM during the study period were included in the study. Meningitis was suspected if the patient was presented with any of the following signs of serious bacterial infection: lethargic, vomiting (≥3 episodes), decreased feeding or inability to breast feed, bulging fontannel (≤2

years), irritable, high-pitched cry, fever [axillary measurement ≥38°C], and headache (above 2 year), meningeal irritation signs (Kernig or Brudzinski signs or neck stiffness, ≥ 1 year). The presence of seizure, impaired consciousness (Blantyre Coma Scale <4 if <9 months of age and <5 if ≥ 9 months of age), signs of raised intracranial pressure, unequal pupils, focal paralysis in any of the limbs, and irregular breathing on examination were considered critical for suspicion of meningitis (54). However, lumbar puncture was attempted to confirm the diagnosis within 2 hours of initiating antibiotic treatment once the infant has been stabilized.

4.3.3.2 Exclusion criteria

- Patients lost to follow within 7 days after starting treatment.
- Children, in whom the initial diagnosis changed to others than BM like fungal, viral after they were included in the study.

4.4 Sample size and sampling strategies

No sampling technique were applied, instead all pediatric cases that fulfilled the illegibility criteria during the study period were recruited in the study.

4.5 Study Variables

4.5.1 Independent variables

Patient related

- Age
- Sex
- Birth weight
- Gestational age
- Mode of delivery
- Immunization status
- Previous history of hospitalization
- Presence of maternal risks during delivery

Disease related

- ❖ Clinical features at/prior to presentation
- ❖ Duration of illness/symptoms before presentation
- ❖ Presence and types of comorbidities during the treatment period

Drug related factors

- Antimicrobial regimens used (initial and any changes) for the entire course of treatment
- Duration to treatment initiation from diagnosis
- Total delay before AB initiation from initial symptoms
- Time to change of empiric ABs
- Number of missed antibiotics doses per treatment
- Adjuvant dexamethasone use and its time of administration in reference to antibiotics

4.5.2 Dependent variables

- ➢ Short-term treatment outcomes

4.6 Data collection procedure and quality assurance

First, the data collectors (two hospital pharmacists) and a supervisor (pharmacist) were trained on how each item would be presented to the patients and extraction of data from patient charts. Since the focus of the study was to see the real picture of the setup, all the data collectors, supervisor and the principal investigator restricted from interfering the management in the ward. They followed each patient twice a day (morning and afternoon) and recorded data that was pertinent to the patient based on the variables on the questionnaires. The supervisor and principal investigator thoroughly followed and coordinated the overall activities.

Pretest was performed on 7 patients in the same ward 2 days before the beginning of the study, but they were not included in the analysis. Frequencies were used to check for entry errors, missed values and outliers. Any error identified was immediately corrected by revising the original data using the unique code**.**

4.7 Statistical analysis

The collected data was entered into Epi data software version 3.1; then exported into and analyzed by using SPSS software for window version 20. Discrete variables are expressed as counts (percentage) and continuous variables as means ± standard deviation (SD) or median and

interquartile range (IQR). All continuous data were categorized based on standard cut off points, or mean / median to fit for logistic regression.

Univariate analysis was done for all independent variables to select possible candidates for multivariate logistic regression and the criterion for selection was $p< 0.25$ from the univariate analysis. Finally, an odds ratio (OR) and 95% confidence interval was used to see the precision of the study and the level of statistical significance was considered at p- value < 0.05. Furthermore, multi-collinearity diagnostic test was performed for all predictors of poor outcomes of childhood BM to see their impact in the regression model and the variance inflation factors (VIF) was used to measure the impact of collinearity among the variables. Hosmer-Lemeshow test was used to see the goodness-of-fit of the logistic regression model.

For the sake of analysis the main treatment outcomes of BM were categorized as good and poor outcomes.

4.8 Ethical considerations

Official ethical clearance was obtained from the college of health sciences institutional review board of JU, and permission from the medical director of the hospital prior data collection. Patient assent was obtained from care givers or family by giving a written letter by 2 languages (Afan Oromo and Amharic) prior data collection. From the very beginning, they were assured that no personal identity would be disclosed, their participation was completely voluntary and that they could be free to withdrew at any time, and this could not affect the medical care that would be given for their child. Above all, the study procedures did not cause any harm to the patient.

4.9 Plans for dissemination of findings

The finding will be presented to Department of Pharmacy, Jimma University and big audience. The finding of this study will be disseminated to: JUSH, JU College of health sciences, Oromia Regional Health Bureau, the Federal Ministry of Health of Ethiopia, and different organizations that work to improve and check the quality of health service delivery in the hospitals of the country like FMHACA. All effort will be made to publish the findings in a peer reviewed scientific Journal.

4.10 Operational definition of terms

- **Young infants:** were defined in this study as those infants under 2 months of age; and **older infants and children:** were those infants and children whose age ranged from 2 months to 14 years based on the treatment protocol (5,8). Therefore, **Pediatrics** according to the current study, included infants and children aged from 1 day to 14 years.
- **Bacterial meningitis** was defined according to physician's clinical diagnosis, including either laboratory-confirmed or probable cases and if no changes in treatment considered until discharge or death to other causes of meningitis like fungal, tuberculosis.
- **Antimicrobials/antibiotics:** are drugs that can halt the growth or kills different microbes. Including drugs (antibacterials, antivirals, antifungals, antiprotozoals, and anthelminthics) (55); however, in this study antimicrobials/antibiotics mean antibacterials.
- **Adjuvant dexamethasone** the use of dexamethasone in patients as an additional to primary antibiotic therapy.
- **Short term treatment outcomes:** according to this study was defined as outcomes of BM detected only until discharge. These included: good and poor outcomes.
    - ✓ **Good outcome-** which means improvement without acute complications
    - ✓ **Poor outcome–** death within the ward, delayed fever, and developed acute neurologic complications during treatment or at discharge.
    - ✓ **Sign of improvement:** normalization of fever was considered as indicator of improvement from BM since fever is the single most common presenting complaint for patients with BM (49). In this study delayed fever was defined as fever persisted for more than 7days (5,8). For afebrile patients other clinical features they presented with were followed for improvement.
    - ✓ **Acute complications:** in the current study it was defined as any complication of BM detected until discharge.
- **Previous history of hospitalization**- patients previously hospitalized in an acute care settings for more than 2 days within 90 days of readmission (56).
- **Maternal risks for the newborn**: was defined as maternal conditions with fever or urinary tract infections within 7 days before delivery (1,2).
- **Lost to follow up: -** intentionally withdrew from the treatment for unknown reason and were discharged against the advice of the health care team.

- **Impaired consciousness status: -** Blantyre coma scale used (BCS 3- 4), and **Comatose:** was defined as a state of altered consciousness in which patient is unresponsive to any environmental stimulus (BCS ≤ 2) (36,53), as assessed by the treating physician.
- **Craniocytosis** the death and unresponsiveness of the cranial nerve cells; examined by imaging studies after initial assessment and treatment (1), examined by the treating physician
- **Hydrocephalus:** was defined as an abnormal increase in head circumference or dilation of the ventricular system as detected by imaging studies (41).
- **Hemiparesis:** paralysis or inability to move one side of the body**;** assessed by the treating physician
- **Quadriparesis:** paralysis or inability to move all four limbs; assessed by the treating physician
- **Hearing impairment:** difficulties in hearing assessed by the treating physician
- **Vision impairment-** difficulties in vision assessed by the treating physician
- **Seizure disorder:** any convulsive disorder of any type that did not exist before the onset of meningitis and was present during and after hospitalization (41).
- **Bulging fontannel**: were examined in children younger than two years old (27)
- **Headache:** was examined in children older than two years (27)
- **Meningeal signs** : were examined in children older than one year of age (27)

5. RESULTS

A total of 693 patients (285 young infants and 408 older infants and children) were admitted to the pediatric ward of JUSH during the study period. Among these, 102 patients diagnosed as meningitis and started treatment for BM. Thirteen patients were excluded from follow up due to the following reasons; 4 lost to follow up before 7 days of treatment, in 2 patients physician decided to stop therapy and in 7 patients diagnosis changed. Therefore, the analysis was done for total of 89 patients that completed the whole course of treatment for BM and die within the ward after initiation of treatments for meningitis.

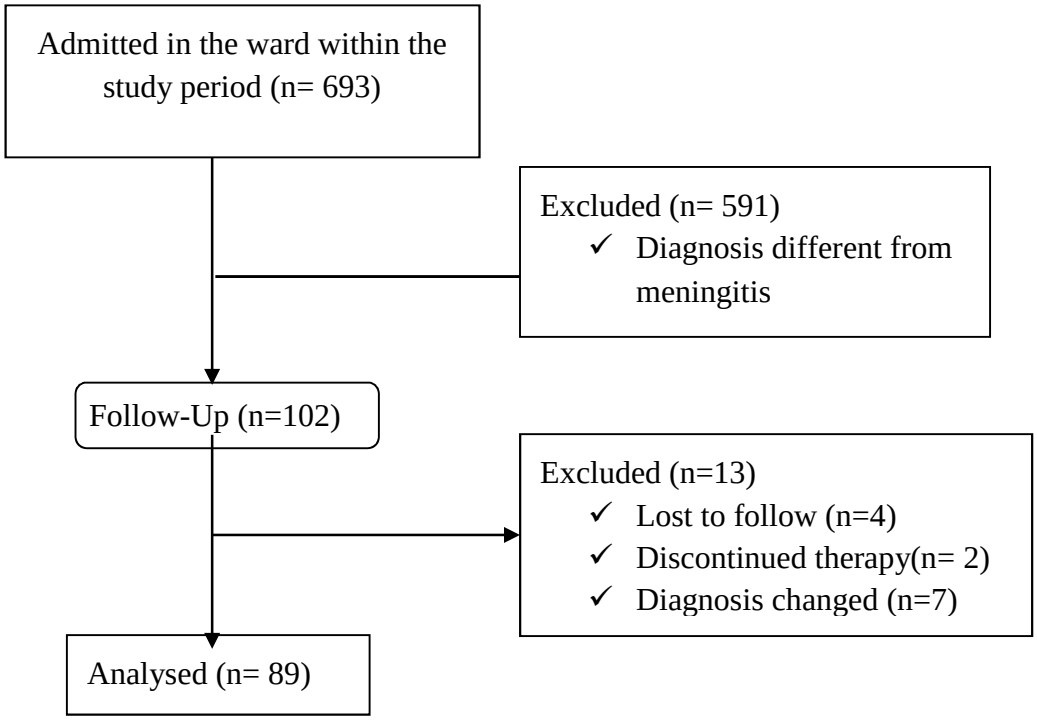

Figure 2 Flow Diagram showing enrollment of children treated for BM in JUSH during February 25- April 29, 2015.

5.1 Demographic and baseline characteristics of the patient

The median age of young infants was 6 days; whereas older infants and children it was 27 month. The proportion of males were higher in both age group; 66% (young infants) and 61.1% (older infants and children). Birth weight was obtained only for 33 young infants (for those delivered in health facilities). Of these, 24.2% were born being under weight (<2.5 kg) (table 2).

Of the children candidate for vaccination according to the national recommendation schedule for immunization, majority (52.8%) were fully vaccinated. Previous history of hospitalization was assessed for all infants and children older than 7 days. Only 3 patients were hospitalized for more than 2 days before readmission in the past 3 months. Maternal history of fever or urinary tract infection (UTI) during delivery was assessed for neonates. Accordingly, 22.6% young infants had maternal history of fever or UTI (table 2).

Table 2 Demographic and baseline characteristics of children treated for BM in JUSH during February 25- April 29, 2015.

Patient characteristics	**≤ 2months (n=53), N (%)**	**>2months (n=36), N (%)**	**Total (n=89) N (%)**
Age, median months (IQR)	0.2(0.03-0.93)	27 (9.8-72.0)	
Gender			
Male	35(66)	22(61.1)	57(64.0)
Female	18(34)	14(38.9)	32(36.0)
Birth weight(kg) , mean (± SD)	2.8 (2.2-3.4)		
≥2.5	25(75.8)		
1.5-2.5	6(18.2)		
≤1.5	2(6.0)		
Gestational age(in weeks)			
>37	37(69.8)		
≤37	12(22.6)		
Mode of delivery			
Vaginal	44(83)		
Caesarian Section	9(17)		
Immunization history			
Fully immunized		19(52.8)	
Not fully immunized		17(47.2)	
Previous history of hospital admission			
Yes	0	3(8.3)	3(3.3)
No	53(100)	33(91.7)	86(96.7)
Maternal history of fever or UTI			
Yes	12(22.6)		
No	41(77.4)		
Median duration of symptoms (hrs.), (IQR)	24 (7.0-72.0)	72 (24-96)	
Mean body temperature (^{0}C) at admission (± SD)	37.6 (36.7-38.5)	38.3(37.4-39.2)	

Table 2 continued…

Lumbar puncture was done	29(54.7)	31(86.1)	60(67.4)
Pneumococci	1(1.9)	2(5.6)	3(3.4)
Meningococci		1(2.8)	1(1.1)
HIb		3(8.3)	3(3.4)
No microorganisms seen	20(37.7)	16(44.4)	36(40.4)
Lumbar puncture failed	24(45.3)	5(13.9)	29(32.6)
No reagent	6(11.3)	11(30.6)	17(19.1)
CSF WBC count was done	26(49.0)	27(75.0)	53(59.6)
CSF WBC count/mm3, median(IQR)	2(0.0-11.2)	2(0.0-12.0)	2(0.0-11.0)
CSF protein analysis was done	10/53	10/36	20(22.5)
CSF protein (mg/dl), median (IQR)	64.0(32.0-128.0)	96.0(28.0-158.0)	80.0(32.0-150.0)
CSF glucose analysis was done	4/53	5/36	9/89(10.1)
CSF glucose (mg/dl), median(IQR)	30.9(14.8-39.8)	32.5(18.9-39.3)	32.5(18.9-39.3)
Presence of comorbidities			
Yes	37(69.8)	21(58.3)	58(65.2)
No	16(30.2)	15(41.7)	31(34.8)
Types of comorbidities			
Sepsis	34(91.9)	6(28.6)	40(44.9)
Malaria		5(23.8)	5(5.6)
Others (pertussis, HIV, impetigo, moderate diarrhea, SAM and anemia)	3(8.1)	10(47.6)	13(14.6)

SD- standard deviation, IQR- interquartile range, UTI- urinary tract infection, HIV-human immunodeficiency virus, SAM-sever acute malnutrition, CSF- cerebrospinal fluid

The median durations of illness before hospital presentation were 24 hours with IQR (7.0-72.0) for young infants whereas, 72 hours with IQR (24.0-96.0) for older infants and children. Likewise, the means body temperature for both groups were almost in the febrile region, 37.6^0C with SD=0.9 for young infants and 38.3^0C with SD=0.9 for those older infants and children (table 2). The two most common clinical features at presentation for young infants were: inability to breast feed (84.9%) and fever (69.8%), followed by vomiting (49.1%) (figure 3). However, the most common features for older infants and children were fever (94.4%) and vomiting (80.6%), followed by headache, decreased feeding and seizure (each 61.1%) (Figure 4).

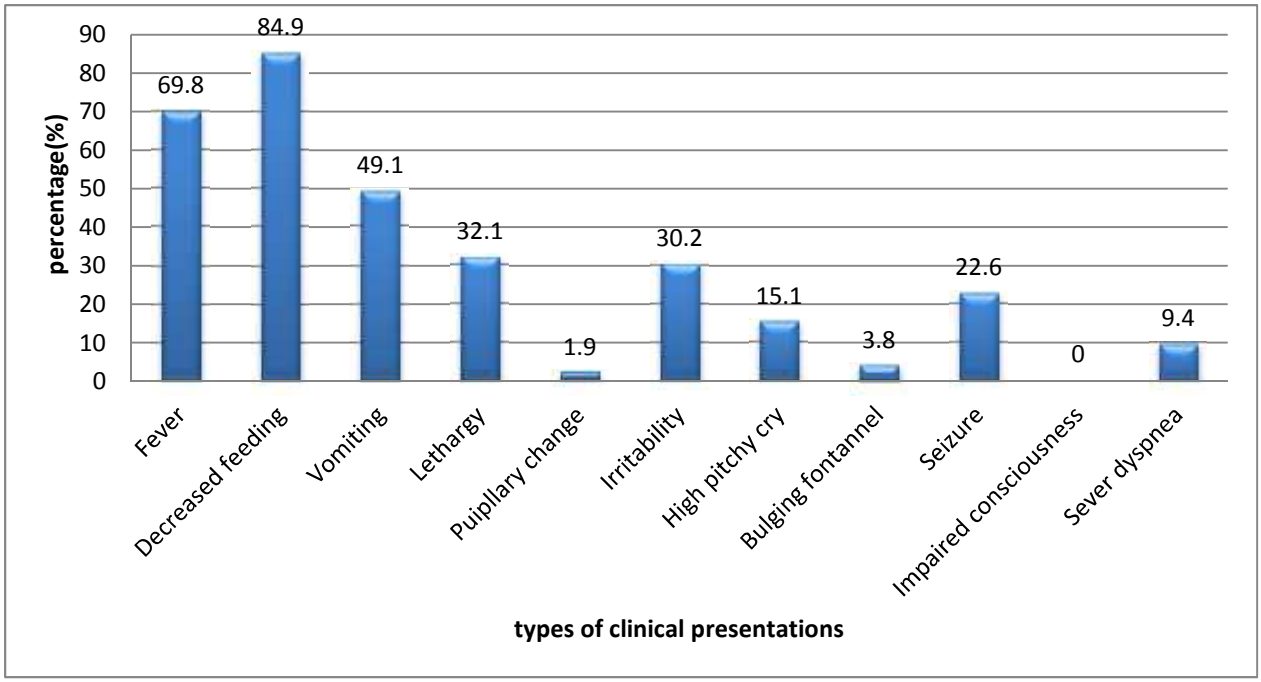

Figure 3 Clinical presentations prior to admission of younger infants treated for BM in JUSH during February 25- April 29, 2015.

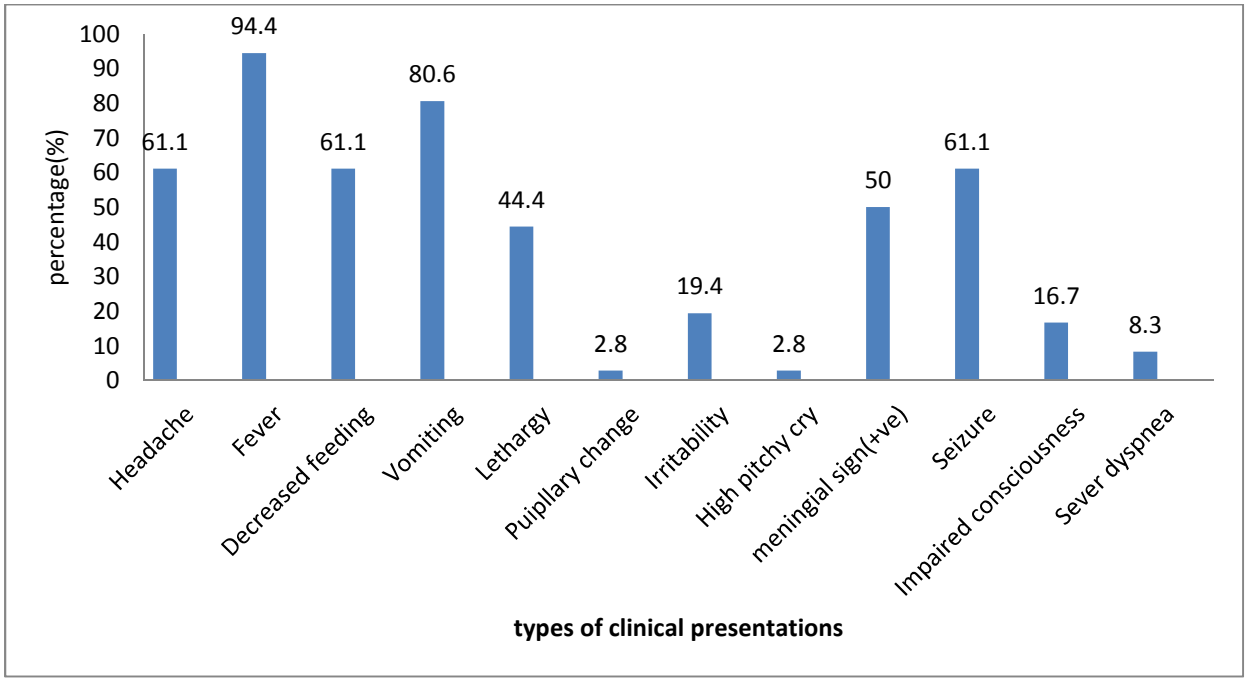

Figure 4 Clinical presentations prior to admission of older infants and children treated for BM in JUSH during February 25- April 29, 2015.

Lumbar puncture was done in 60 patients (67.4%) and failed in the remaining 29 (32.6%) of cases. Among these, the causative pathogens were identified by CSF stain only in 7 patients (7.9%): 3 pneumococcal, 3 HIb and 1 meningococcal. In 36 patients (40.4%), the result was reported as 'no microorganism was seen', and in the remaining 17 patients (19.1%) there were no reagents to carry out the stain. Cerebrospinal fluid WBC count was performed in 53cases (59.6%); majority being in the normal range with median of 2 cells/mm3 (0-11). The CSF protein analysis results were reported in 20 patients (22.5%) having the median value of 80.0 mg/dl (32.0-150.0) which was lower than bacterial range CSF protein level. However, CSF glucose was analyzed only in 9 patients (10.1%) with the median of 32.5mg/dl (18.9-39.3) that was within the bacterial range CSF glucose level (table 2).

The overall incidence of meningitis was 14.4% (figure 2). Most of the young infants (69.8%) had comorbidities, mainly of sepsis (34/37); whereas in older infants and children comorbidities of different types observed in 58% of the cases (table 2).

5.2 Drug related factors

Most of the young infants (86.8%) were initially treated with empiric Ampicillin plus Gentamycin regimen. On the other hand, in majority of the older infants and children (66.7%), the initial AB regimen was Crystalline penicillin plus Chloramphenicol. The median duration of treatment from diagnosis for both age groups was the similar, 1.0 hour with IQR (0.5-2.0). By considering delayed presentation and delay in hospital for treatment, these two durations were added to give another important factor, delay for treatment from initial illness. Therefore, the median delay for treatment from initial illness was 32 hours (10.2-73.5) for young infants, whereas 73 hours (25.4-98.4) for older infants and children. Meanwhile in the course of treatment, in 20% of patients ABs changes were considered, while the remaining 80% completed the entire course of treatment with their initial regimens. The mean duration of AB change for younger infants was 5 days with SD= 3, whereas 3.2 days with SD=1.8 for older infants and children (table 3). During the course of treatment, 23 patients missed at least one dose of ABs; the main reason (87%) for missing being unaffordability. Dexamethasone was given for 44.4% of children above 2 months of age (table 3).

Table 3 Drug regimen used in children treated for BM in JUSH during February 25- April 29, 2015.

Regimens		**Under 2 months (n=53), N (%)**	**Above 2 months (n=36), N (%)**
Initial regimen	Ampicillin plus Gentamycin	46(86.8)	1(2.8)
	Ceftriaxone plus Gentamycin	7(13.2)	9(25.0)
	Crystalline Penicillin plus Chloramphenicol	-	24(66.7)
	Ceftriaxone alone	-	2(5.6)
Regimen changed to	Ceftriaxone plus Gentamycin	13(24.5)	-
	Ceftriaxone alone	-	2(5.6)
	Ceftazidime plus Vancomycin	2(3.8)	1(2.8)
Median duration (hours) to treatment from diagnosis(IQR)		1 (0.3-3.0)	1 (0.5-2.0)
Mean duration to AB change (days, ± SD)		5(2.0-8.0)	3.2 (1.4-5.0)
Median delay of treatment from initial illness(IQR)		32(10.2-73.5)	73(25.4-98.4)
Number of AB doses missed	1 or 2	8(66.7)	9(25.0)
	≥ 3	4(33.3)	2(5.6)
Reasons for missing	Unaffordability	9(75.0)	11(100)
	IV line unavailable	3(25.0)	0
Dexamethasone use		-	16(44.4)
Duration to dexamethasone with reference to ABs	At same time or within 20 minutes before ABs	-	10(62.5)
	Beyond 20 minutes or after ABs	-	6(37.5)

SD- standard deviation, IQR- interquartile range, CSF- cerebrospinal fluid

5.3 Treatment outcomes of childhood BM

The median duration to improvement after treatment were 6 days (3.0-9.2) for young infants, whereas 4 days (3.0-7.0) for older infants and children. Almost 72% of the young infants and

61% of older infants and children improved within 7 days of treatment. Totally, 67.4% of the patients improved without acute complication; while, 9% died, 18% had delayed fever and 5.6% had acute neurologic complications during the course of treatment. The observed acute neurologic complications were hemiparesis and recurrent seizures in 3 patients, hearing impairment in 2 patients, and quadriparesis, craniocytosis, and visionary impairment each in a patient (table 4).

Table 4 Treatment outcomes of children treated for BM in JUSH during February 25- April 29, 2015.

Patients Outcomes		**For ≤2months (n=53)**	**For >2months (n=36)**	**General (n=89)**
		N (%)	**N (%)**	**N (%)**
Good outcomes/improved		38(71.7)	22(61.1)	60(67.4)
Poor outcomes	Death	3(5.7)	5(13.9)	8(9.0)
	Delayed fever	10(18.8)	6(16.7)	16(18.0)
	Acute neurologic complication	2(3.8)[b]	3(8.3)[c]	5(5.6)
Median time to improvement (days, IQR)		6(3.0-9.2)	4(3.0-7.0)	5(3.0-8.5)

[b] quadriparesis (1) & craniocytosis (1), [c] hemiparesis and recurrent seizures (3 patients), visionary impairment (1patient), hearing impairment (2patients)

In general, a total of 69 patients (77.5%) improved, 8 (9%) died, 5 (5.6%) referred for further management of the neurologic complications, and 7 (7.9%) withdrew from the treatment with delayed fever (poor condition) for unknown reason. Out of 16 patients with delayed fever (table 4), 9 patients later improved due to further management and supportive care given within the ward (table 5).

Table 5 General status at discharge of children treated for BM in JUSH during February 25-April 29, 2015.

Statuses at discharge	Young infants (n=53)	Older infants & children (n=36)	General (n=89)
	N (%)	N (%)	N (%)
Improved	44(83.0)	25(69.4)	69(77.5)
Died	3(5.7)	5(13.9)	8(9.0)
Neurologic complication (referred)	2(3.8)[b]	3(8.3)[c]	5(5.6)
Lost to follow up with delayed fever	4(7.5)	3(8.3)	7(7.9)
Median time to death in days, (IQR)			5.0(3.25-6.00)
Median hospital stay in days (IQR)	14(10-16)	12(9-15)	13(10-15)

[b] quadriparesis (1) & craniocytosis (1), [c] hemiparesis and recurrent seizures (3 patients), visionary impairment (1patient), hearing impairment (2patients)

5.4 Risk factors and predictors of poor outcomes of BM

Risk factors of poor outcomes for young infants and that of older infants and children might be different since they were exposed to different treatment regimens. Therefore, separate analysis were done for the two groups and presented as follows.

I) Risk factors for poor outcomes of BM in young infants

Univariate logistic regression was done for all independent variables to select possible candidates for multivariate logistic regression.

In order to determine their association with the incidence of poor outcomes, 5 potentially relevant predictors were chosen for multivariate analysis based on their significance from the univariate analysis with $p < 0.25$. These were: (1) male gender, (2) mode of delivery, (3) sever dyspnea, (4) any antibiotic changes and (5) number of AB doses missed. There were no missing data on the 5 variables selected. Among the five possible risk factors, multivariate logistic regression identified only one, any antibiotic change to be an independent predictor of the poor outcomes (table 6).

Table 6 Univariate and multivariate logistic regression of risk factors for poor outcomes of BM in young infants (n=53) in JUSH during February 25- April 29, 2015.

Variables		**Outcomes**		**Univariate results**		**Multivariate**	
		Good (n=38)	**Poor (n=15)**	**p-value**	**COR(95% CI)**	**AOR(95% CI)**	**p-value**
Age	≤7 days	20	9	.628	1.350(.401-4.543)		
	>7 days	18	6				
Sex	**Male**	**27**	**8**	**.224**	**.466(.136-1.598)**	0.285 (.068-1.193)	.086
	Female	**11**	**7**				
Birth weight (kg)	≤1.5	1	1				
	1.5-2.5	2	4	.054 [a]	2.551(.984-6.618)		
	≥2.5	19	6				
Gestational age	< 37 weeks	7	5	.254	2.222(.564-8.759)		
	≥ 37 weeks	28	9				
Mode of delivery	**CS**	**5**	**6**	**.038**	**4.400(1.008-17.790)**	2.015 (.292-13.907)	.477
	Vaginal	**33**	**9**				
Maternal history of fever or UTI	Yes	8	4	.822	1.200(.245-5.886)		
	No	12	5				
Duration of illness	>24 hours	17	7	.899	1.081(.326-3.585)		
	≤ 24hours	21	8				
Fever	Yes	26	11	.726	1.269(.335-4.814)		
	No	12	4				
Decreased feeding	Yes	32	13	.822	1.219(.217-.842)		
	No	6	2				
Vomiting	Yes	19	7	.827	.875(.264-2.897)		
	No	19	8				
Lethargic	Yes	13	4	.597	.699(.186-2.634)		
	No	25	11				
Pupillary change	Yes	0	1	1.000	---		
	No	38	14				
Irritability	Yes	12	4	.726	.788(.208-2.989)		
	No	26	11				
High pitchy cry	Yes	6	2	.822	.821(.146-4.606)		
	No	32	13				
Bulging	Yes	2	0	.999	---		

Table 6 continued…

fontannel	No	36	15					
Seizure	Yes	8	4	.661	1.364(.341-5.447)			
	No	30	11					
Impaired consciousness	Yes	0	0	---	---			
	No	38	15					
Sever dyspnea	**Yes**	**2**	**3**	**.122**	**4.500(.670-30.230)**	5.335	(.567-50.209)	.143
	No	36	12					
Presence of comorbidities	Yes	26	11	.726	1.269(.335-4.814)			
	No	12	4					
Initial AB regimen	Ceftriaxone plus Gentamycin	4	3	.336	2.125(.414-10.903)			
	Ampicillin plus Gentamycin	34	12					
Time to treatment from diagnosis	>1 hour	16	7	.763	1.203(.362-4.001)			
	≤ 1 hours	22	8					
Time to treatment from initial illness	>32 hours	18	8	.696	1.270(.383-4.206)			
	≤ 32 hours	20	7					
AB changes considered	**Yes**	**8**	**7**	**.069**	**3.281(.913-11.796)**	**4.425**	**(1.007-19.440)**	**.049**
	No	30	8					
Duration to AB change	>72 hours	3	3	.833	1.250(.158-9.917)			
	≤ 72 hours	5	4					
Missed ABs	**1 or 2 doses**	**5**	**3**			3.708	(.615-22.364)	.153
				.036	**2.853(1.071-7.601)**			
	≥ 3 doses	**1**	**3**			12.088(.967-151.128)		.053
	Never	32	9					

[a] Variable with >10 % missing data, AOR= adjusted odds ratio, COR= crude odds ratio

II) Predictors for poor outcomes of BM in young infants

Fifteen patients out of 53 young infants treated for BM (28.3%) had poor outcomes. Of which 3/53(5.7%) died, 10/53 (18.9%) had delayed fever and 2/53 (3.8%) developed acute neurological complications (each patient developed craniocytosis and quadriparesis) (table 4). Sixty six percent (35/53) of young infants treated for BM were males (table 2). The occurrence of poor outcomes in young infants was less likely for males compared to females, but it was not statistically significant. (AOR= 0.285, 95% CI (0.068-1.193)). Delivery assisted by caesarian section was done in 31% infants under 2 months of age (table 2). Infants whose delivery aided by caesarian section experienced 2 fold risks of poor outcomes than those delivered vaginally, however the difference was not statistically significant, AOR= 2.015, 95% CI (0.292-13.907).

Only 5 patients (9.4%) presented with sever dyspnea among young infants (table 2). Patients with severe dyspnea prior admission were 5 times more likely to have poor outcomes than those without sever dyspnea (AOR= 5.335, 95% CI (0.567-50.209)), however no significant difference observed between the two.

In young infants the frequently used initial regimen was Ampicillin plus Gentamycin (86.8%), while only 13.2% of patients were given Ceftriaxone plus Gentamycin for initial management (table 3). Initial AB regimens were either changed or modified only in 15 patients (28.3%) of this age group. Most of the AB changes were modifications of the initial Ampicillin plus Gentamycin to Ceftriaxone plus Gentamycin (13/15, 86.7%), whereas in only 2 cases the initial AB regimen was changed to Vancomycin plus Ceftazidime (13.3%). The risks of experiencing poor outcomes was highly associated with changing the initial ABs than completing the whole course of treatment with the initial ABs with AOR= 4.425, 95% CI (1.007-19.440). During the course of treatment, 12 patients (22.6%) missed at least one dose of their ABs (table 3). Of these: 8 patients missed 1 or 2 doses and 4 patients missed 3 or more doses. Missing 1 or 2 doses of the prescribed ABs was found to increase the risk of experiencing poor outcomes as compared to patients who never missed their entire doses of ABs, however the difference was not statistically significant with AOR=3.708, 95% CI (0.615-22.364). Missing 3 or more doses also increased the occurrence of poor outcomes compared to those who never missed their entire doses of ABs, but statistical significant difference was not observed too, AOR= 12.088, 95% CI (0.967-151.128).

III) Risk factors for poor outcomes of BM in older infants and children

Univariate logistic regression was done for all independent variables to select possible candidates for multivariate logistic regression.

The following seven candidates were selected based on their p-value from univariate analysis results. Factors with $p<0.10$ were selected, because the sample size for this age group was small (n=36) to allow higher p-value (<0.25) that would include more candidates. There were no missing data for all the seven selected variables. These were: (1) male gender, (2) irritability and (3) seizure prior to admission, (4) presence of any comorbidity, (5) initial AB regimen with Ceftriaxone plus Gentamycin or Ceftriaxone alone instead of Crystalline penicillin plus Chloramphenicol, (6) longer than 1 hour delay to treatment initiation from diagnosis and (7) missing one or more doses of AB during the treatment course. From the seven potential risk factors multivariate logistic regressions determined the following four independent predictors of poor outcomes of BM: (1) irritability and (2) seizure prior admission, (3) initial AB regimen with Ceftriaxone plus Gentamycin instead of Crystalline penicillin plus Chloramphenicol, and (4) missing 1or 2 doses of AB during the treatment course compared to patients never missed.

Table 7 Univariate and multivariate logistic regression for risk factors for poor outcomes of BM for older infants and children (n=36) in JUSH during February 25- April 29, 2015.

Variables		**Outcomes**		**Univariate results**		**Multivariate**	
		Good (n=22)	**Poor (n=14)**	**p-value**	**COR(95% CI)**	**AOR(95% CI)**	**p-value**
Age	≤ 12 months	6	4	.932	1.067(.240-4.740)		
	> 12 months	16	10				
Sex	**Male**	**16**	**6**	**.079**	**.281(.068-1.157)**	.123(.003-5.890)	.289
	Female	6	8				
Previous history of hospitalization	Yes	2	1	.837	.769(.063-9.371)		
	No	20	13				
Vaccination status	Not completed	9	8	.344	1.926(.496-7.485)		
	Completed	13	6				
Duration of illness	>72 hours	5	6	.207	2.550(.596-10.917)		
	≤ 72 hours	17	8				
Headache	Yes	14	8	.336	.286(.022-3.669)		
	No	1	2				
Fever	Yes	20	14	.999	---		
	No	2	0				
Decreased feeding	Yes	14	8	.697	.762(.194-2.996)		
	No	8	6				
Vomiting	Yes	18	11	.811	.815(.153-4.347)		
	No	4	3				
Lethargic	Yes	8	8	.225	2.333(.593-9.176)		
	No	14	6				
Pupillary change	Yes	1	0	1.000	---		
	No	21	14				
Irritability	**Yes**	**2**	**5**	**.065**	**5.556(.901-34.246)**	**38.388(1.777-829.357)**	**.020**
	No	20	9				
High pitchy cry	Yes	0	1	1.000	---		
	No	22	13				
Meningeal sign	Positive	11	7	.946	1.061(.191-5.903)		
	Negative	5	3				
Seizure	**Yes**	**11**	**11**	**.095**	**3.667(.797-16.863)**	**27.529(1.451-522.346)**	**.027**
	No	**11**	**3**				
Impaired conscious	Yes	2	4	.144	4.000(.623-25.679)		

Table 7 continued…

ness	No	20	10				
Sever dyspnea	Yes	1	2	.327	3.500(.286-42.769)		
	No	21	12				
Presence of comorbidities	**Yes**	**10**	**11**	**.057**	**4.400(.955-20.274)**	8.413(.430-164.664)	.160
	No	**12**	**3**				
Initial AB regimen	**Ceftri+ Genta**	**3**	**6**			**66.480(3.157-1400.127)**	**.007**
				.013	**6.963(1.518-31.933)**		
	Ceftriaxone	**0**	**2**			---	
	Cryst. pen+ CAF	18	6				
Duration to treatment from diagnosis	**>1 hour**	**6**	**8**	**.079**	**3.556(.864-14.629)**	1.985(.076-52.162)	.681
	≤ 1 hour	16	6				
Delay to treatment from initial illness	> 73 hours	8	8	.225	2.333(.593-9.176)		
	≤ 73 hours	14	6				
AB changes considered	Yes	1	2	.327	3.500(.286-42.769)		
	No	21	12				
Duration to AB change	>3 days	0	1	1.000	---		
	≤ 3 days	1	1				
Missed ABs	**1 or 2 doses**	**4**	**5**			**47.329(2.141-1046.186)**	**.015**
				.034	**4.284(1.113-16.483)**		
	≥ 3 doses	0	2			---	
	Never	18	7				
Dexamethasone use	Yes	8	8	.271	2.167(.547-8.586)		
	No	13	6				
Time to dexamethasone	> 20 minutes or after	2	4	.309	3.000(.361-24.919)		
	≤ 20 minutes	6	4				

Ceftri=ceftriaxone, genta=gentamycin, cryst.pen=crystalline penicillin, CAF= chloramphenicol, AOR= adjusted odds ratio, COR= crude odds ratio

IV) Predictors of poor outcomes of BM in older infants and children

Among the 36 older infants and children treated for BM, 14 patients (38.9%) experienced poor outcomes. Death occurred in 13.9% of patients, delayed fever in 16.7%, and acute neurologic complications in 8.3%. The observed acute neurologic complications were hemiparesis and recurrent seizures (in 3 patients), visionary impairment (in 1 patient), hearing impairment (in 2 patients) (table 4).

Majority (61.1%) of older infants and children treated for BM were males (table 2). Lower incidence of poor outcomes of BM was observed in males compared to females with (AOR= .123, 95% CI 0.03-5.890); but the difference was not statistically significant. In older infants and children clinical presentations characterized by irritability was 19.4% and seizure 61.1% at admission (table 2). Patients who had an irritable clinical feature prior to admission were at nearly 38.4 times more increased risks of poor outcomes than those without this feature (AOR=38.388, 95% CI (1.777-829.357)). Seizure prior admission was also found to be associated with about 27.5 times increased incidence of poor outcomes compared to patients who had not seizure prior admission (AOR= 27.529, 95% CI (1.451-522.346)).

Twenty one patients among older infants and children (61.1%) had different types of comorbidities. Of these 6 patients (28.6%) had sepsis, 5 patients (23.8%) had malaria, and 10 patients (47.6%) had either of pertussis, HIV, impetigo, moderate diarrhea, SAM and/or anemia (table 2). Even though the presence of comorbidities was not statistically significant its presence seemed to increase the incidences of poor outcomes (AOR= 8.413, 95% CI, (0.430-164.664)).

In older infants and children the most commonly used initial AB regimen was Crystalline penicillin plus Chloramphenicol (69.4%). Ceftriaxone plus Gentamycin and Ceftriaxone alone were also the other initial AB regimens given to patients of this age group in 25% and 5.6% of patients respectively (table 3). Initial regimen with Ceftriaxone plus Gentamycin was found to be strong predictor of poor outcomes (p=0.007). As compared to patients who initially treated with Crystalline penicillin plus Chloramphenicol, those initially treated by Ceftriaxone plus Gentamycin were highly associated with increased incidence of poor outcomes (AOR =66.480, 95% CI (3.157-1400.127)). However, longer than 1 hour delay to treatment from diagnosis failed to show statistically significant association with poor outcomes (AOR= 1.985, 955 CI (0.076-52.162)). During the course of treatment 11 patients (30.6%) missed at least one doses of their

prescribed ABs. Of these 9 patients missed either 1 or 2 doses, while the remaining 2 patients missed 3 or more doses (table 3). Patients who missed either 1 or 2 doses of ABs during the entire course of treatment were found to be at about 47 times more risks of experiencing poor outcomes compared to those never missed their doses (AOR= 47.329, 95% CI(2.141-1046.186)).

6. DISCUSSION

Early initiation of an optimal antibiotic therapy for confirmed or suspected BM, pending the CSF results, has been shown to be one of the most important factor to reduce morbidity and lethality (4,5,9,10,54- 57). In the current study, most of the young infants (86.8%) were initially treated with empiric Ampicillin plus Gentamycin regimen. On the other hand, in older infants and children, the most commonly used empiric AB regimen was Crystalline penicillin plus Chloramphenicol (66.7%) followed by Ceftriaxone plus Gentamycin (25%). The selection and timing of initiation of ABs were in line with the current recommendation for developing countries (5). The choice of ABs was also similar with studies conducted in some resource limited settings (36,41,48). The median duration of treatment from diagnosis for both age groups was the similar, 1.0 hour. This was similar with the study from Italy (1 hour) (48) and even better than that from Uganda (9.6 hours)(42).

Meanwhile in the course of treatment, in 20% of patients ABs changes were considered due to poor response to the empiric regimen. Among young infants for whom ABs change were considered, in most (87%) of the cases the empiric Ampicillin plus Gentamycin was modified to Ceftriaxone plus Gentamycin, and only 3 patients the regimen changed to Ceftazidime plus Vancomycin. The change was also in agreement with current recommendation as almost all the changes were made to the first line alternative considering affordability as per the recommendation for resource limited countries of WHO (5). Guidelines and current evidence recommend narrowing of the empiric regimen as soon as the agent is identified (5,10,56), or change of empiric ABs within 2-3 days in cases if it is not possible to identify the agent and the patient is not improving with the empiric ABs (5). However, the duration to change of ABs in our case was very longer than the recommended. The mean duration of AB change for young infants was 5 days while it was 3.2 days for older infant and children.

Generally, nearly 67% of patients treated for BM improved within 7 days of treatment without acute complications and the median time for improvement was 5 days. This was better than a study done in Uganda in that time to improvement from initiation of treatment was 10.3 days (42). The difference could be due to delayed presentation (median=6.5days) and late initiation of treatment (median=9.6hours) from Uganda's study compared to median time to hospital presentation was only 2 days and median time to treatment was only 1 hour in the current study.

The cumulative incidence of poor outcomes in this study was 32.6%; including mortality of 9%, acute neurologic complications (6%), and delayed fever in 18% of patients (table 4). The incidence of poor outcomes was almost comparable with most studies from resource limited settings (19,23,36,41,59) but it could be slightly lower than those reports since only the short-term treatment outcomes were included and had no follow up after discharge that would increase the rate of both mortality and neurologic complications in those studies.

In all young infants, combinations of two ABs were considered as empiric therapy for BM. Most of the patients (86.8%) were given combination of Ampicillin and Gentamycin, and the remaining 13.2% were put on Ceftriaxone plus Gentamycin for initial management. Among patients initially put on Ampicillin plus Gentamycin, almost 85% improved without complications and 15% had poor outcomes while in patients initially treated with combination of Ceftriaxone and Gentamycin, about 71% improved without acute complications 29% experienced poor outcomes. The patients initially treated with Ceftriaxone plus Gentamycin experienced comparatively more poor outcomes, as those patients initially presented with severe clinical feature (seizure) at admission.

The incidences of poor outcomes within 7 days of treatment were different when the two age groups compared; nearly 28% for the young infants versus 39% for the older infants and children (table 4). Majority of the older infants and children (57%) presented to the hospital lately (after 2 days of illness), whereas only 36% of young infants presented after 2 days. However, this difference in delayed presentation with age was not statistically significant on univariate analysis (COR=2.3, p= .061). The median age of the young infants was 6 days which might indicate most the young infants were born within the hospital and started treatment immediately as they got ill compared to those older infants and children who came to the hospital after the disease got advanced. Furthermore, majority of the older infants and children (59%) had severity characterized by seizure before admission compared to only 23% of those patients under 2 months (COR=4.9, p=0.001). Therefore, the higher percentage both by late presentation and severe clinical features before admission could contribute to more incidences of poor outcomes among older infants and children than young infants.

6.1 Predictors of poor outcomes in young infants

In young infants, despite the percentage of males treated was quite higher (66%) and those had poor outcome still higher (53%), the risk of experiencing poor outcomes seemed lower compared to females, but this failed to show statistically significant association in multivariate logistic regression. In the same manner, caesarian section aided delivery initially seemed to increase the risk of poor outcomes compared to vagina delivery, however it was not found to be one of the important predictors of poor outcomes.

In the present study, the presence of severe dyspnea at admission was found to increase the risk of poor outcomes; but statistically significant association with poor outcomes was not determined under multivariate logistic regression. This was similar to the study of Pelkonen T. et al in which severe dyspnea before admission showed a non-significant increase in the risks of developing severe neurological sequelae and significantly increased the risk of death (39).

Young infants for whom empiric AB changed were associated with increased incidence of poor outcomes than those completed their entire course of treatment with the initial AB regimen. First of all, patients for whom ABs changed were those critically ill or those did not improving to the empiric regimen. Secondly, the mean duration for AB change was 5 days which was much longer than the recommended (2-3 days)(5). Furthermore, most of the patients (93%) who ABs were changed, had one or more comorbidities. Therefore, the higher percentage of comorbidities in patients who had AB changes could have contributed to the poor outcomes as the difference was significant on univariate logistic regression ($p=0.026$), and the longer duration of time to AB changes could also have contributed too. In addition, in some studies it was highlighted that most of the patients in developing countries have delayed presentation to the higher health care settings having been treated with common 3rd generation cephalosporins (mainly Ceftriaxone) without a definite diagnosis in primary or private settings (22,41). Consequently, these could have its own impact on the sensitivity of the pathogens to these antibiotics, but this needs further investigation. Even though statistically significant difference was not observed, missing one or more doses of the prescribed ABs had increased the risk poor outcomes in the current study. As the main reason for missing was unaffordability, really this needs intervention by improving effective communication of the health care team with patients' family or care givers and facilitating the opportunities for them on how to get alternative cost effective therapies.

6.2 Predictors of poor outcomes in older infants and children

In this study, despite the gender distribution was predominated by males (61%), female gender had contributed a higher percentage (57%) to the poor outcomes of BM. Interestingly; this gender difference was not statistically significant. Delayed presentation to the hospital (after 72 hours of illness) was higher in females (36%) versus 27% in males. Ahmed A. in his study at Gonder and Hawassa highlighted that, there are still social and cultural factors that favor easier access for males to the healthcare facilities as compared to the females and even those females that attend the health care facilities are after the disease got advanced/complicated (11). This may also highlight the bias or the preference that may be given by the family to the male children over the female children which need further research.

Many clinical features prior to or at hospital admission are associated with the outcome of bacterial meningitis (12,23,25-27,30-40). In the current study, irritable feature at presentation found to increase the incidence of poor outcomes, as this feature is mostly manifestation of CNS disorders characterized by abnormal sensitivity signifying the advanced nature of the disease. Similarly, the presence of seizure at or prior to admission was associated with increased incidence of poor outcomes. This is in line with different studies in which the occurrence seizure prior hospital admission increased mortality (36,42,43) and sever neurological squealae (39,41-43), as the occurrence of seizure at presentation indicates the advanced stage (complication) of the disease (34).

About 58% of older infants and children treated for BM had one or more comorbidities. These included sepsis in 6 (29%) patients, malaria in 5 (24%), and in 10 children other comorbidities (like pertussis, HIV, impetigo, moderate diarrhea, SAM and/or anemia). The incidence of poor outcomes was 39% and there were consistently increased incidence of poor outcomes, in both univariate and multivariate logistic regression, in patients who had one or more comorbidities though it was not statistically significant. The possible explanation could be most of these comorbidities were clinical suspicions due to the similarity of clinical features like sepsis and malaria with that of BM rather than laboratory confirmation. Another possible reason that needs further evaluation was; probably there could be proper management of these comorbidities though the management was not presented here. This was similarly not significant in the study of Prishtina (Kosovo) (43).

The most commonly used initial AB regimen in older infants and children was Crystalline penicillin plus Chloramphenicol (66.7%) followed by combination of ceftriaxone and gentamycin (25%). Out of the 24 patients (66.7%) initially treated with Crystalline penicillin plus Chloramphenicol, 79.2% improved without acute complications and the remaining 20.8% had poor outcomes. However, among 9 patients (25%) that were initially given a combination of Ceftriaxone and Gentamycin, almost half (44.4%) experienced poor outcomes. Initial regimen with Ceftriaxone plus Gentamycin instead of the first line Crystalline penicillin plus Chloramphenicol significantly increased the risk of poor outcomes. First of all, the main indication for selection of Ceftriaxone based regimen instead of first line penicillin/ampicillin based regimen in the ward was severity (critically illness) at presentation. Secondly, in majority (75%) patients initially put on Ceftriaxone plus Gentamycin the initial dose of the drugs was administered lately (after 1 hour of diagnosis) compared to only in16% of patients on Crystalline penicillin plus Chloramphenicol the drugs were initiated lately (after 1 hour of diagnosis). The reason for delay could be due to searching of this expensive drug (Ceftriaxone compared to Penicillin) since it is not commonly available in our wards. Thirdly, there was higher percentage of patients with comorbidities during the course of treatment 67% for ceftriaxone based against 53% for penicillin based. Besides, the use of adjuvant dexamethasone was lower (33% versus 54%) and not fully vaccinated were higher (78% versus 33%) in patients on Ceftriaxone based regimen compared to patients on Penicillin based regimen respectively. Therefore, the increased incidence of poor outcomes among patients on Ceftriaxone based regimen than those on Penicillin should not be surprising in the presence of all of the above factors that could contribute to the poor outcomes.

However, in a Cochrane review of randomized controlled trials (RCTs), the effectiveness and safety of Ceftriaxone or Cefotaxime were compared with conventional treatment with Penicillin or Ampicillin plus Chloramphenicol in patients with community-acquired acute bacterial meningitis. No clinically important difference between Ceftriaxone or Cefotaxime and conventional antibiotics was identified (61). Pelkonen T. et al in the study among the Sub-Saharan Africa children also showed the evidence that supported the finding of Cochrane review above in that, treatment with ceftriaxone instead of with the primary regimen of Penicillin plus Chloramphenicol, did not improve the prognosis (39).

On the other hand, the report from KOSOVO showed that, risk for developing neurologic complications and mortality was very high in patients treated with the initial antimicrobial therapy using Ceftriaxone alone or with Chloramphenicol than those initially treated with Penicillin G alone or with Chloramphenicol (58). Similarly, Theodoridou K. et al also reported that, third-generation cephalosporins were related to an increased risk of hydrocephalus and ventriculitis, and the use of Penicillin was found to have a protective effect against neurologic squealae (41). The strength of the last study in showing higher rate of neurotoxicity associated with cephalosporins compared to penicillins is that, it used multinomial logistic regression to identify the association among the different AB regimens with specific types of neurologic complications. But the current study used binomial logistic regression in that the association with neurotoxicity was not clearly known.

In the current study, another factor related to ABs found to have statistically significant association with poor outcomes was number of missed ABs dose. Patients who missed one or more doses of their prescribed ABs experienced more pronounced poor outcomes than those never missed their ABs dose. As it was mentioned above under young infants section, this could highlight the need of intervention by narrowing the gap between the health care team and patients' family or care givers by working together and searching for all possible options for the benefit of the patients.

6.3 Limitations of the study

Our study was not free of limitation and needs precaution in interpreting. To mention some: the study period was short due to time limitation which couldn't allow collecting enough sample size. As could be seen from the result part, some of the ranges of confidence intervals were wider due to small sample size. In addition, it would have been better if the patients were followed for some time after discharge to get the full impacts of the disease so that complete outcomes could be measured. Because of that sever neurologic squealae could not be detected within this short period; instead the data was limited to short-term acute complications.

The other important factor common to most resource limited settings was lack of availability of some important laboratory facilities in which most of the cases in the current study were not confirmed by laboratory evidence, instead on the clinical diagnosis which may be less accurate than the laboratory assisted one. In addition, patients and families/care givers were unable to differentiate antibiotics from other medications when they were asked about their previous use of ABs before admission. So, due to fear of the incompleteness of the data for such variables they were removed from the questionnaire after pretest.

Lastly, lack of studies regarding sensitivity of causative agents to the existing antimicrobials in our setups could impact treatment as well as comparisons of the regimens in this study.

7. CONCLUSION

In the current study the selection of empiric therapy, change of empiric regimen as well as timing of antimicrobials for treatment of childhood BM was almost consistent with recommendations for resource limited settings except that timing of empiric antibiotics change was much longer. This could highlight the need for revising management protocol regarding timing of empiric ABs for children with BM in this ward.

At discharge nearly one-fourth of the patients treated for BM experienced poor outcomes implicating the need of further attention while treating these patients.

Finally, some independent predictors of poor outcomes were identified. In young infants, change of empiric antibiotics during the course of treatment was found to independently predict the incidence of poor outcomes. Whereas, in older infants and children, sever clinical presentations characterized by irritability and seizure prior hospital admission and drug related factors including initial treatment with combination of Ceftriaxone and Gentamycin instead of first line Crystalline penicillin plus Chloramphenicol and missing one or more doses of the prescribed antibiotics during the course of treatment were found to independently increase incidence of poor outcomes. These could also signify that the need of antimicrobial sensitivity testing the specified ward.

8. RECOMMENDATIONS

- **To the hospital (JUSH)**
  - To create awareness on the health care team to give due attention for patients presented with sever clinical features like seizure and irritability as these were the alarming signs of poor outcomes
  - To follow and strengthen effective communication between the health care team and patients (family/care givers) since their non-compliance (missing their prescribed ABs doses) was found to implicate poor prognosis. As this can be solved by improving the interaction between the patient (family/care givers) and the health care team to create common understanding for the benefit of patient thereby searching for and facilitating all the possible options for the patient (family/care givers) on how to get the cost effective alternatives in scenario.
- **To researchers**
  - Further study with large sample size and longer study period are required
  - Studies focused on antimicrobial sensitivity are also needed

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ANNEXES

1. Patient Information Sheet

Name of the Principal investigator: Habtamu Acho

Name of study area: Jimma University Specialized Hospital, paediatric ward

Research Budget covered by: Jimma University

Research objective: To assess the current use of antimicrobials and determine treatment outcomes in children with bacterial meningitis, in JUSH pediatric ward.

Significance of the study: The study finding will be used to help improve management of meningitis in children in this department.

Study procedure: The data collectors will extract data from patient chart and interview patients' caregivers using questionnaires after obtaining consent from the patients' care giver.

Risks: No risks

Participant role: volunteerism and helping in providing information to the data collectors during the interview.

Participant right: They have a right to stop the interview at any time, or to skip any question that he/she does not want to answer.

Beneficial: The study is beneficial for patient's quality service delivery for future encounters.

Incentives: Participants will not be provided any specific incentive for taking part in the research other than acknowledgment.

Confidentialities: The study result will not include patient's name and address and information specific to the patient will not be shared with the medical team or any others.

Agreement: Patients' caregivers are expected to be fully voluntary to participate in the study.

Whom to contact: If you have any kind of inconveniencies about the study, you can contact :

- Habtamu Acho (principal investigator)
  - Tel: 0931999546
  - Email: achuhab31@gmail.com

2. Written Assent

Name of principal investigator: Habtamu Acho (Jimma University)

Research title: antimicrobial use and treatment outcomes of childhood bacterial meningitis in paediatric wards of Jimma University Specialized Hospital

Card number_____

Unique code number_____

1. I confirm that I understand the information sheet for the above study and have had the opportunity to ask questions.
2. I understand that my participation is completely voluntary and that I am free to withdraw at any time, without giving any reason, without my child's medical care or legal rights being affected.
3. I understand that my medical notes will be looked at by data collectors of this study and necessary information will be extracted. I give permission for these individuals to have access to my records.
4. On behalf of my child I agree to take part in the above study.

I would like to confirm my agreement by signing.

Name of participant (caregiver)_____Signature_____ date_____

Name of the data collector: _____signature:_____date_____

Name of the principal investigator: Habtamu Acho Signature: _____ date_____

Thank you for your participation and Co-operation!

Barefammaa eeyyamma

- **Maqa isaa qo'anna gagessu**: Haabtamuu Achoo
- **Mataduree qo'annoo:** faayyadammaa dharraa lubbuwwaan ijaan hin argaamne fibu'aa yaallii ijoolleewwaan ji'a lama gaddii menenjayitasi waardii ijoollee Hospitalaa addaa Univeersitii Jimmaa

  Lakk. kaardii _____

  Lakk. Kodii _____

1) Oddeeffannoo qo'annoo kana huubachuu koo naan mirkanessa caara gaaffiwwan kana gaafachuu lee argadheerraa.
2) Hirmaanan koo gutummaa gututti fedhii koo irratti akkani hunda'e naaf gaalerraa yoo naati hintoole saababbaa male tajajjiili muca kootif kenemu uttuu hinhubamiin dhise demmuu akkan danda'u naan bekka.
3) Akka kaardiin mucakooti odeffenoo qo'annoo kanaf wara sasabanin akkani illalamu fiodeffannon barbachisoo ta'an akka kessaa fudhatamu naaf gala. Kanafuu anni eyyamma issanif kenu koo naan mirkanessa.
4) Muccaa koo bakkaa bu'udhaan qo'anno kana irratti naan hirmaadha.

Waaligaltee koo maalatoo kottin ibsuu naan fedhaa.

- Maqa issaa qo'annoo irrattii hirmaatu (waarra muccaa) _____ maalattoo_____
- Maqa issa qo'annoo gegessuu_____ maalattoo_____ guyyaa_____
- Maqa issaa odeffaannoo funanu: Haabtamuu Achoo maalattoo_____ guyyaa_____

Gargarsaafi irratti hirmaana gotaanif gaalani kenyaa guddadha

የፈቃደኝነት መጠየቂያ

- **ጥናቱን የሚያካሀደው ተማሪ:** ሀብታሙ አጮ (ጅማ ዩኒቨርሲቲ)
- **የጥናቱ ርዕስ:** የፀረ_ተህዋስያን መድኃኒት አጠቃቀም እና የህክምናው ውጤት በማጅራት_ገትር ታመው በጅማ ዩኒቨርሲቲ ስፔሻላይዝድ ሆስፒታል ህፃናት ዋርድ በተኙት ጨቅላ_ህፃናት(ሁለት ወር በታች) ላይ

የካርድ ቁጥር : _____

የሚስጥር ቁጥር : _____

1. ከላይ በርዕሱ የተገለጸውን የጥናት አላማ ተረድቸዋለሁ።በቃለ_ምልልሱ ወቅት ማንኛውንም ጥያቄ መጠየቅ እንደምችልም አውቀያለሁ።
2. ለዚሁም ጥናት የተሳተፍኩት በፈቃደኝነት ሲሆን በማንኛውንም ሰዓት በቃለ_ምልልሱን ማቋረጥ ብፈልግ የምችል መሁኑንና ይህንንም በማድረጌ በህፃኑ/ኗ ላይ ምንም የሚደርስ አደጋ አለመኖሩንና የህክምናውም ሁኔታ በዝሁ ምክኒያት የማይቀየር መሆኑንም ጭምር በግልጽ በማወቅ ነው።
3. የህፃኑ/ኗ የህክምና መረጃ በመረጃ ሰብሳቢዎች ዘንድ በሚስጥር የሚጠበቅ መሆኑን በማወቅ መረጃውን እንዲጠቀሙ ፈቅጃለሁ::
4. ህፃኑ/ኗን በመወከል የተሳተፍኩ መሆኔን ከዚህ እንደሚቀጥለው በፊርማዬ አረጋግጣለሁ።

- የህፃኑ/ኗ ተወካይ (አሳካሚ) ስም : ———————————ፊርማ ————ቀን ————————
- የመረጃ ሰብሳቢው ስም: ———————————— ፊርማ ————ቀን ————————
- ጥናቱን የሚያካሀደው ተማሪ ስም : ሀብታሙ አጮ ፊርማ ————ቀን ————————

በፈቃደኝነት መረጃውን ለመስጠት ስለተባበሩን በጣም አመሰግናለሁ !

3. Questionnaires

1. Patient related

- Card No. _____
- Unique code:_____
- Date of admission: _____
- Age (days):_____
- Sex: male ___ Female___
- Current weight(kg): _____
- Birth Weight(kg): if you remember it:_____
- Mode of delivery:
  a) Vaginal : _____
  b) Caesarean section: _____
- Gestational age(months):_____

❖ Was the infant hospitalized in an acute care unit for 2 or more days before readmission? Yes ☐ No ☐

❖ Did the mother have UTI or fever within one week before delivery? ☐ ☐

2. Disease related

Clinical sign and symptoms on admission	Mark(√)	Laboratory Tests	Done(√)	Results
➢ Headache	☐	Tests		
➢ Fever (> 38 ^{0}C)	☐	CSF Gram Staining	☐	Negative ☐ Positive ☐
➢ Poor feeding	☐			
➢ Vomiting	☐	CSF Cell Count	☐	CSF Cell count: _____ /mm3
➢ Lethargy	☐			
➢ Pupillary change	☐	CSF Proteins	☐	Protein conc: _____mg/l
➢ Irritability	☐			
➢ high-pitched cry	☐	CSF Glucose	☐	Glucose _____ mg/dl
➢ Bulging Fontanel	☐	Others		Microbiology:
➢ Positive meningeal sign	☐	- culture		

❖ Presence of complication on admission
  a) impaired consciousness ☐
  b) Seizures ☐
  c) sever dyspnea ☐

❖ Duration of illness:_____

❖ Physician assessment/diagnosis:_____

3. Drug related

Duration(day)	Drugs used/ name		Time to first AB dose from admission(ms*)	Strength(mg/Kg)	Frequency	Total daily dose
D1	Initially					
D2						
D3						
.	Added if any					
.						
.						
	Antibiotics changed					

*ms= minutes, D= day, tt= treatment, AB=antibiotic

Number of AB doses missed**:**_____

4. Treatment outcomes

- Death: Yes ☐ No ☐
- Fatal Case Date: _____
- Lost to follow up: Yes ☐ No ☐
- Discontinued treatment: Yes ☐ No ☐
- Date of discharge: _____
- Hospital stay(days): _____

- Development of acute complications until discharge: If yes (√)
  - a) Blindness/impaired vision ☐
  - b) seizure ☐
  - c) Hearing impairment ☐
  - d) Quadriparesis and/or paresis ☐
  - e) Hydrocephalus requiring a shunt ☐

- Time to Vital signs and symptoms improvement

Date	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 8	D 9	D 10	D 11	D 12	D 13	D 14	D 15	D 16	D 17	D 18	D 19	D 20	D 21
T(^{0}C)																					
V																					
PF																					
IR																					
BF																					
L																					
AC																					
HPC																					
PC																					
S																					

Key D=date from admission, V= vomiting, PA= poor feeding, IR= irritable, BF= bulging fontannel, L=lethargy, AC=altered consciousness, HPC= high-pitched cry, PC=pupillary change, seizure

Data Collected By: _____

Cross Checked By: _____