From the

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Assessment of Treatment Strategies in Acute Bacterial Meningitis in Ethiopia

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Abstract

Background – Management of patients with suspected bacterial meningitis needs swift clinical decision making and early antibiotic initiation. However, the care of such patients in resource limited settings is challenging due to patients' late presentation, limited diagnostic facilities and lack of evidence based treatment guidelines.

Objective – To investigate the current strategies in the management of bacterial meningitis and to assess its discharge outcomes at teaching hospitals in Ethiopia

Methods – Retrospective and prospective study designs were used. In the retrospective study, data was collected at four teaching hospitals in Ethiopia from patients who were treated as a case of bacterial meningitis from December 31, 2011 to April 30, 2015. The prospective study was conducted at Jimma University Hospital from March 1, 2013 to December 31, 2015. Descriptive analyses were done for most of baseline characteristics. Bivariate and multivariable analyses were also done to identify factors associated with unfavorable outcomes.

Result – (i) *Retrospective study*: 425 patients of age 14 years and older were included in this study. Lumbar puncture was done for only 236 (55.5%) of cases. Only 96 (22.6%) of them had cerebrospinal fluid (CSF) abnormalities compatible with bacterial meningitis. A causative bacterium was identified in only 14 of the cases. Overall, 86 patients (20.2%) died while in the hospital. (ii) *Prospective study*: 127 adults (≥18 years) participated in this study; 109 (85.8%) had their CSF analysed. However, only 90 (70.9%) of them had findings suggestive of bacterial meningitis and causative bacteria were isolated in only 26 (20.5%). The over all in hospital mortality was 22.8% (29 deaths). Depressed level of consciousness, focal neurologic deficits and concomitant pneumonia on presentation were associated with increased in hospital death.

Adjunctive dexamethasone treatment was used in 50.4% and 33.1% in retrospective and prospective studies, respectively, and was associated with unfavorable discharge outcome.

Conclusion – Outcome in patients treated for bacterial meningitis in Ethiopia was found to be poor. Moreover, most of them did not receive proper diagnostic workup and alternative diagnoses were overlooked as a result. Adjunctive dexamethasone treatment was associated with unfavorable outcome at discharge. Thus, management of patients with suspected bacterial meningitis should be supported by laboratory tests and treatment should be tailored to evidences from the settings and current evidence-based recommendations.

Key words – Bacterial meningitis, treatment, outcome, dexamethasone, Ethiopia, Africa

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Abbreviations and acronyms

BF – Blood film

BM – Bacterial meningitis

CBC – Complete blood count

CT – Computed tomography

CNS – Central nervous system

CSF – Cerebrospinal fluid

ESR – Erythrocyte sedimentation rate

GCS – Glasgow coma scale

GOS – Glasgow outcome scale

Hb – Haemoglobin

HIV – Human Immunodeficiency Virus

ICP – Intracranial pressure

LAMA – Left against medical advice

LAT – Latex agglutination test

LOS – Length of (hospital) stay

LP – Lumbar puncture

MMSE – Minimental state examination

PMN – Polymorph nuclear cells

SAH – Subarachnoid haemorrhage

SBM – Spontaneous bacterial meningitis

TBM – Tuberculous meningitis

WBC – White blood cells

WHO – World Health Organization

1. Introduction

Bacterial meningitis (BM) is a very serious infection and a common cause of death and disability worldwide (1). Patients with BM are usually seriously ill and often present soon after symptom onset (2, 3). The classic clinical presentation of acute bacterial meningitis consists of fever, nuchal rigidity, and mental status change (1). However, in adults presenting with community-acquired acute bacterial meningitis, the sensitivity of the classic triads is low (4), but almost all of them present with at least two of the four symptoms of headache, fever, neck stiffness, and altered mental status (2, 3).

Majority of cases of BM are caused by *Neisseria (N.) meningitidis*, *Streptococcus (S.) pneumoniae*, and *Haemophilus (H.) influenzae* (2, 5-7). *Listeria (L.) monocytogenes* is a common cause of bacterial meningitis in patients over 50 years of age or those who have deficiencies in cell-mediated immunity (8).

The mortality and long term neurological sequelae associated with bacterial meningitis remain high even in the era of advanced antibiotic therapy and nursing care (2, 7, 9). In addition to factors associated with the host and pathogen (2, 9), the duration of disease and timing of antimicrobial treatment are important determinants of outcome (10). Thus, the management of acute bacterial meningitis needs swift clinical decision making and early commencement of antibiotics (11, 12). Evidence of brain infection and identification of causative organisms should be settled through cerebrospinal fluid (CSF) analysis (13).

Despite having the highest burden of BM in the world (14), sub-Saharan Africa is least equipped to deal with this important public health problem (3). Low health seeking behaviour, shortage of health workforce and underdeveloped health infrastructure (15) are important constrains to achieving these goals. Diagnostic facilities are limited and appropriate treatment modalities are difficult to access in primary hospitals in these settings (3).

Evidenced based local guidelines for management of BM are also limited in the continent. As a result, management of patients with BM in most settings in Africa is based primarily on clinical grounds without confirmatory test for causative bacteria (16). For these reasons, BM presents an exceptional challenge to physicians working in resource-limited settings.

1.1. Bacterial meningitis: a global health issue

Bacterial meningitis is one of the most common infectious diseases throughout the world today (17). Globally, it is estimated that at least 1.2 million cases of bacterial meningitis occur every year, most of them in developing countries. The global reported cases of BM are attributable to invasive meningococcal disease due to its occurrence as an outbreak causing approximately 135,000 deaths per annum throughout the world (14, 18). It is at least ten times more common in developing countries than in the rest of the world (19). The mortality is also higher in such settings (7, 16, 20) due to limited diagnostic facility and antibiotic options (3). Additional factors such as advanced HIV infection (3, 21), malnutrition (22), and the emergence of antibiotic-resistant bacteria (23, 24), complicate the management of the infected patient. For these reasons, bacterial meningitis presents an exceptional challenge to physicians working in low income settings (3).

About 80% of all cases of bacterial meningitis are caused by *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* (3, 17, 25). However, the relative frequency of isolation of various bacterial species as a cause of meningitis varies with age, and among geographical regions (17). The major causes of community-acquired bacterial meningitis in adults in developed countries are S. *pneumoniae* and *N. meningitidis* whereas *H. Influenzae* is commonly seen in meningitis of the paediatric age group (2). *L. monocytogenes* is common cause of bacterial meningitis in patients over age 50 to 60 years or those who have deficiencies in cell-mediated immunity (8).

Patients with bacterial meningitis are usually quite ill and often present soon after symptom onset. Depending on the study, the median duration of symptoms before admission is often only 24 hours (ranging from one hour to 14 days) (2). The classic clinical presentation of bacterial meningitis consists of fever, nuchal rigidity, and mental status change (1). However, in adults presenting with community-acquired bacterial meningitis, the sensitivity of the classic triads is low (4), but almost all present with at least two of the four symptoms of headache, fever, neck stiffness, and altered mental status (2, 3, 26).

Despite advances in antibiotic therapy and nursing care, the mortality and long term neurological sequelae associated with bacterial meningitis remain high (9). Determinants of the pace of bacterial meningitis are related to both host and microbial virulence factors. The duration of disease (27), age (28) and immune status of the patient (29, 30), timing of

antibiotic initiation (26, 31), and type of microorganism (20, 32) are important factors in determining the outcome of bacterial meningitis.

The strongest risk factors for an unfavorable outcome are those that are indicative of systemic compromise, a low level of consciousness, and infection with S. pneumonia (2). In general, the risk of death from bacterial meningitis increases with decreased level of consciousness on admission, onset of seizures within 24 h of admission, signs of increased intracranial pressure (ICP), age >50, the presence of comorbid conditions including shock and/or the need for mechanical ventilation, and delay in the initiation of treatment (1, 31).

The overall mortality is highest for pneumococcal meningitis, with neurological morbidity affecting half of the survivors (33, 34). In-hospital mortality rates are 25% for *S. pneumoniae*, 10% for *N. meningitidis*, and 21% for L. monocytogenes (1). Generally speaking, any form of bacterial meningitis that is untreated or treated very late in its course is almost uniformly fatal (31).

Neurologic sequelae are common in survivors of bacterial meningitis. Moderate or severe sequelae occur in ~25% of survivors. Common sequelae include decreased intellectual function, memory impairment, seizures, hearing loss and dizziness, and gait disturbances (35).

Morbidities and mortalities related to bacterial meningitis are said to increase in patients with HIV infection (36, 37). Even in the highly active antiretroviral therapy era, the risk of developing spontaneous bacterial meningitis (SBM) is 19 times higher among HIV-1-infected patients than among uninfected ones (36). SBM in HIV-1-infected patients carries a worse prognosis than in uninfected ones both in terms of lethality and sequelae (36, 37). Neurologic complications are three times as common and overall case fatality ratio is four times higher than non-HIV infected counter parts (36).

Bacterial meningitis poses more challenge in sub-Saharan Africa than any part of the world. The continent has some of the highest rates of bacterial meningitis in the world (38). The burden of the problem is intensified by frequent outbreak of meningococcal meningitis in the region (39). Meningococcal meningitis is highest in the African meningitis belt that extends from Senegal in the west to Ethiopia in the east (Figure 1). The region consists of 26 countries in sub-Saharan Africa (25). Over a span of 20 years from 1995 to 2014, total of 900,000 cases of meningococcal meningitis were reported in these countries with 10%

fatalities and 10-20% documented neurological sequelae. The most recent large scale outbreak in the region occurred in 2009 in Niger and Nigeria with over 4,000 reported deaths (40).

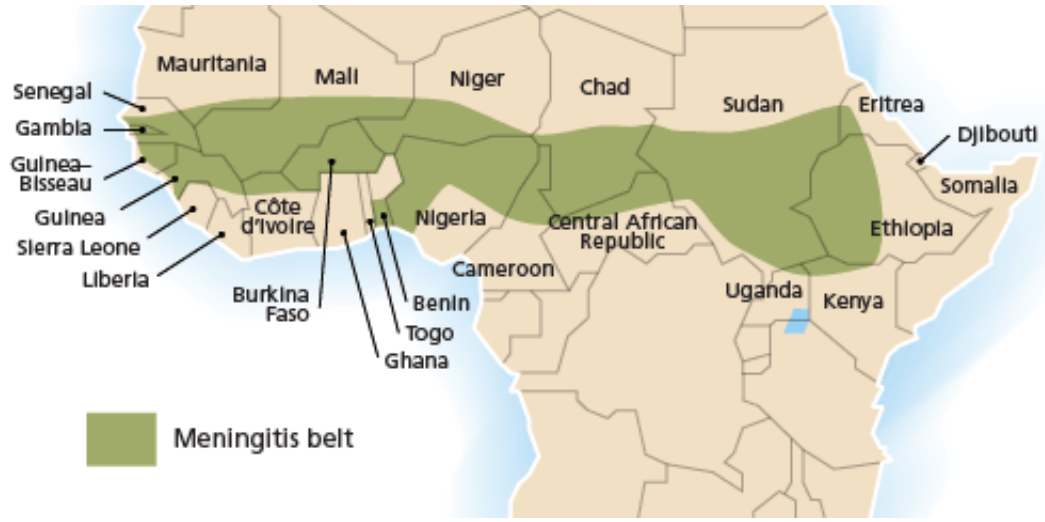


Figure 1-1 – The African Meningitis Belt
Source: *Control of epidemic meningococcal disease, WHO practical guidelines, 1998, 2nd edition.* (25)

In addition to the burden of the problem, case management of bacterial meningitis is one of the great challenges of health care system in Africa and other low income countries (3). Diagnostic facilities are limited and appropriate treatment modalities are hardly accessible in these areas. Evidence based management guidelines are in short supply and hence treatment options are often derived from western data. As a result, the mortality and neuropsychological sequelae associated with the disease are highest in this part of the world (38).

In conclusion, bacterial meningitis poses more problems in low income settings and in sub-Saharan Africa in particular due to frequent occurrence of meningococcal meningitis, limited diagnostic facility and antibiotic option, and lack of evidence based guidelines. As a result management of patients with the problem in the setting is challenging.

1.2. Bacterial meningitis in Ethiopia

Ethiopia is one of the countries in the WHO African meningitis belt (25). Most documented data regarding epidemiology of bacterial meningitis in adults in Ethiopia are limited to surveillance and outbreak reports for meningococcal meningitis. Documented meningitis outbreak in Ethiopia dates back to 1901 with major outbreaks occurring almost every decade

in the 20th century (41). The country recorded the largest outbreaks in 1980's with reported mortality of over 1600 in 1989 alone (41, 42). However, the country is still having frequent small scale outbreaks throughout the country (41, 43-45).

Information regarding sporadic bacterial meningitis in the country is scarce. A study in paediatric age group revealed that *H. influenzae*, *S. pneumoniae* and *N. meningitidis* account for about 90% of the cases (46). Findings in adults showed predominance of *N. meningitidis* and *S. pneumoniae*. These studies also showed that the isolation rate of causative bacteria was between 5 and 10% of those suspected with bacterial meningitis (44, 47). A significant proportion of those who presented to the hospital were treated with one or more antibiotics for the same complaint before admission (48).

The morbidities and mortalities related to meningitis in Ethiopia are also immense. Epidemiological studies in Ethiopia found the fatality rates for meningococcal meningitis and meningococcemia to be 16% and 85% respectively (42). In another study, a quarter of children treated for meningitis were found to have hearing loss at discharge (49). However, the overall epidemiology of the disease remains poorly understood due to lack of data from well-designed studies.

As a result, the overall incidences and spectrum of complications, and prognostic factors in adults with bacterial meningitis in Ethiopia is not well known. In addition to this, poor health service system has made care of patients with meningitis to be extremely challenging. Diagnosis is based mainly on clinical grounds and treatment is entirely pragmatic.

Patients' late presentation due to multiple factors, scarce laboratory facilities, limited antibiotic options, underdeveloped infrastructure to access health service, scarce number of health workforce, and most importantly, lack of clear cut national strategy for care of patients with meningitis are further setback. Moreover, the sensitivity and specificity of the signs and symptoms of bacterial meningitis has never been validated in the country and evidences regarding antibiotic susceptibility pattern is extremely scarce.

The aim of this study was thus to identify specific critical points that need be addressed to improve medical workup and treatment of patients with bacterial meningitis in this country.

2. Objectives

As it has been highlighted earlier, data regarding the burden of the problem and clinical evidences for development of treatment guidelines for bacterial meningitis in Ethiopia is limited. Addressing these important gaps is key step in the direction of improving case management of patients with the disease. The main purpose of this project was to assess the current diagnostic and treatment strategies in the management of adult patients with bacterial meningitis in Ethiopia. The goal is to create a scientific basis for developing guidelines for the diagnosis and treatment of meningitis in rural parts of Ethiopia where resources are limited.

2.1. Objectives of the study

General objective

To assess treatment strategies and outcome in adult patients with suspected bacterial meningitis admitted to teaching hospitals in Ethiopia.

Specific objectives

1. To evaluate strategies used to diagnose and treat bacterial meningitis in Ethiopia
2. To identify the common causes of bacterial meningitis in the setting
3. To assess treatment outcome at discharge
4. To investigate factors associated with unfavorable discharge outcomes

2.2. Major research questions

1. What are the major clinical presentations of patients with suspected BM?
2. How was the diagnosis established? (Clinical only? CSF analysis? Microbiologically confirmed?)
3. What are the common bacterial etiologies?
4. How were the patients treated? (Antibiotic choice? any adjunctive treatment? were the patients treated for other differential diagnoses?)
5. What is the outcome at leaving hospital (death or neurologic sequelae)?
6. What are the major factors associated with unfavorable outcomes?

3. Methods

This research project employed two types of research design: retrospective data collection and prospective follow-up of patients admitted with presumptive diagnosis of bacterial meningitis. The methods employed by each design will be detailed as follows.

3.1. Retrospective study

3.1.1. Study setting

This study was conducted at four teaching hospitals in Ethiopia – Jimma University Specialized Hospital, Hawassa University Referral Teaching Hospital, University of Gondar Hospital and Arba Minch Hospital. The first three are full-fledged university hospital serving as referral hospitals. Arba Minch hospital is a general hospital affiliated with Arba Minch University's medical school. All of these hospitals are located in the meningitis belt of Africa – Gondar in the northwest, Jimma in the southwest and Arba Minch and Hawassa in the south (**Figure 2**). Moreover, all serve the regions which have reported outbreaks of meningococcal meningitis in the last ten years (43-45). The overall catchment population for the four hospitals is nearly 25 million – over a quarter of the Ethiopian population.

The diagnosis of bacterial meningitis in the country is based mainly on clinical manifestations and microscopic findings of the CSF. Patients suspected with meningitis undergo lumbar puncture procedure unless there are contraindications. As routine CT scanning for such patients in Ethiopia is not available, contraindications for the procedure are based on clinical judgement only. Accordingly, those with focal neurologic deficits at presentation, papilledema, and significantly depressed mentation (GCS <5/15) do not undergo the procedure.

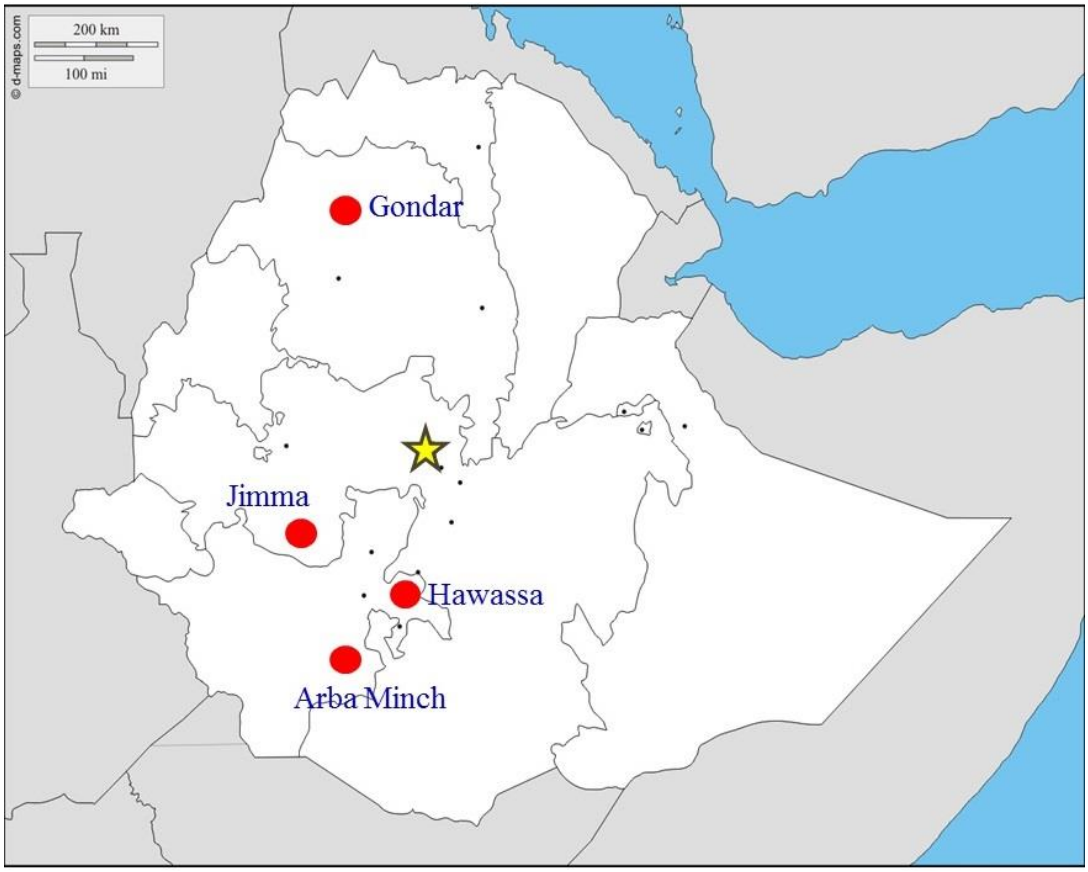


Figure 3-1– Location of Teaching Hospitals included in the study

3.1.2. Study participants

Patients included in this study were those of age 14 years and older treated with a presumptive diagnosis of bacterial meningitis during the period of January 1, 2011 to April 30, 2015. Only patients who had complete medical records regarding issues related to diagnosis, treatment and outcome of BM were included in the study. Patients whose antibiotic treatment was discontinued before ward admission because of confirmed alternative diagnosis were excluded.

Definition of the cases – Cases treated as bacterial meningitis were categorized according to their clinical presentation and CSF findings based on the 2003 World Health Organization case definition used in WHO-recommended surveillance standards for surveillance of selected vaccine-preventable diseases (50). These categories are:

1. *Suspected unproven cases of bacterial meningitis* – Cases with sudden onset (≤7days) of fever (axillary temperature of ≥38.0°C) PLUS any of: neck stiffness and altered consciousness PLUS no other alternative diagnosis PLUS no or incomplete CSF analysis.

2. *Possible bacterial meningitis* – A case with clinical signs as described for "suspected unproven BM" PLUS CSF examination showing at least one of the following three – (1) Turbid appearance (2) Pleocytosis (>100 white cells/mm3) (3) Pleocytosis (10-100 white cells/mm3) AND either an elevated protein (>100 mg/dl) or decreased CSF to serum glucose ratio (< 40%).

3. *Confirmed (proven) bacterial meningitis* – Cases with detected microorganisms from CSF specimen by one or more of the following methods: culture, gram stain microscopy or latex agglutination test.

4. *Non-cases* (diagnosis of bacterial meningitis doubtful or less likely) – Cases not fulfilling any of the above criteria and/or those with evidences suggesting other diagnoses.

3.1.3. Data collection procedures

Patients treated as cases of BM were identified using the data from inpatient registration books of medical wards at each hospital. Using six digit medical registration numbers, patients' records were retrieved from the archives for data collection. The data was collected by a standardized case report form (see **Annex – 1**). The information gathered included socio-demographic profiles, presenting clinical signs and symptoms, CSF findings and other laboratory results, the applied treatment regimens, clinical course in the hospital, and discharge conditions (death and neurologic sequelae).

The data was collected by general practitioners and medical residents after they were trained for one day about data collection procedures.

The data was between February 1, 2015 and May 31, 2015.

3.1.4. Outcome measurements

The status of the patient at leaving the hospital (death, regular discharge or self-discharge) was retrieved from treating physician's document. Any reported death along its possible immediate causes was reviewed from death summary document. The discharge note was reviewed to find out if there were any neurologic sequelae at leaving hospital. As there was no routine assessment of GOS at the hospitals, the data was obtained from discharge or death summary attached in patient's medical chart. The scales were elaborated based on physician's record as: 1=if death was documented; 2=if patient was in 'coma' or 'unresponsive' at leaving hospital; 3=if document included any of 'hemiparesis', 'paraparesis', or 'major disability'; 4=if document included 'facial palsy 'or if any milder neurologic deficits were

reported – such as ‘decreased hearing capacity’; 5=if document included ‘full recovery’ or ‘improved’. The scores were dichotomized into favorable (5) and unfavourable (1 to 4) outcomes.

3.2. Prospective study

3.2.1. Study setting

The prospective study was conducted at Jimma University Specialized Hospital (JUSH). It is the only teaching hospital in southwest Ethiopia with catchment population of over 15 million. It is located in Jimma town, 352 km southwest of the capital Addis Ababa. The town is situated in the meningitis belt of Africa.

There was no bacteriology unit at Jimma University hospital before. The service was established at the hospital as part of this project and is functional since 26 October, 2013. Microbiologic analyses of CSF specimen using microscopy of gram stain specimen, latex agglutination test (LAT) and culture with antibiotic susceptibility tests are part of routine care for BM at the hospital now. Dr Andreas Wieser from Max von Pettenkofer-Institute for Hygiene and Clinical Microbiology of Ludwig Maximilians-University, Munich led the designing and establishment of the unit. He also served as the lead microbiologist of the unit during the first six months and also gave on service training for local staffs.

Figure 3-2 – Bacteriology Unit of Jimma University Specialized Hospital (*Established October 2013*)

3.2.2. Study participants

Participants in this group were those with suspected bacterial meningitis and 18 years or older at the time of hospital admission. In general, participants included in this group fell into four categories based on likelihood of bacterial meningitis (inclusion criteria used).

I. **Bacterial meningitis with proven/confirmed etiology**

Patients with clinically suspected BM supported by confirmed etiology by one or more of these methods: culture, gram stain microscopy or latex agglutination test.

II. **Bacterial meningitis with unidentified (Unknown) etiology**

Patients with at least three of the following four CSF findings: (i) Turbid CSF, (ii) ≥1000 white cells/µL, (iii) Protein >100mg/dl and (iv) CSF to serum glucose ratio of <0.4 WITHOUT detection of causative bacteria from CSF.

III. **Possible bacterial meningitis**

a. Abnormal CSF but not fulfilling the above criteria (WBC ≥100 but <1000 or WBC>10 PLUS glucose ratio<0.4 PLUS protein>100).

b. Where LP was not possible due to contraindications or technical problems, patients with all of these symptoms (fever> 39^0C, nuchal rigidity, mental status change) lasting 7 days or less since on set **PLUS** negative blood film for Plasmodium falciparum where included.

Patients in both 'a' and 'b' were included only if diagnosis other than bacterial meningitis was found to be less likely on clinical examination and laboratory.

IV. **Bacterial meningitis less likely –** they were patients empirically treated by treating doctor as BM with full course of antibiotics though the evidence supporting its diagnosis was lacking. These cases were separated into two subgroups:

a. Alternative (other differential) diagnosis possible – they were cases with the following characteristics: (i) clear evidences of brain insult (body weakness, seizure, impairments of consciousness, nuchal rigidity) (ii) clinical presentations atypical for BM, e.g., long duration of symptoms (>1 week); absence of triads of BM; or symptoms suggestive of other diseases (iii) CSF findings not compatible with bacterial meningitis described in 'I' to 'III' above or suggestive of or confirmatory of alternative diagnosis.

b. Non-cases (doubtful cases) – cases not fulfilling any of the above criteria: (i) no clear evidence of brain affection AND (ii) normal CSF findings.

Exclusion: - Those with proven chronic meningitis of any cause

- Those with posttraumatic meningitis
- Patients with prior residual neurologic deficit lasting less than 3 months
- Symptomatic chronic psychiatric disorders

All patients who fulfilled the inclusion criteria and willing to participate on the study were recruited consecutively.

3.2.3. Data collection procedures

The data study was conducted from March 1, 2013 to December 31, 2015 (34 months). The data was collected by using pretested structured questionnaire specifically prepared for this study (see **Annex – 2**). Patients, the guardian if patient was unconscious, were asked for consent before data collection. **Figure 3.3** shows flow chart for evaluation of patients from admission to discharge.

Admission assessment – The initial interview was done by the treating physician to obtain information regarding demographic profiles (age, gender, and residence), duration of illness and symptoms at presentation. Physical examination was done at presentation by the same person to assess general condition, vital signs, mental status, signs of meningitis (nuchal rigidity, Kerning's sign, Brudzinski's sign), and presence of neurologic deficit.

Collection and processing of CSF specimen – Lumbar puncture, in the absence of contraindication, was done under possible aseptic condition for all patients with suspected BM to collect CSF specimen. This was done as soon as it was possible (before antibiotics administration). However, if the LP was not possible within an hour of presentation or consideration of diagnosis of BM, patient was given first dose of antibiotics and CSF collection was done within 24 hours of this. About 2-3 ml of CSF specimen was collected in two separate sterile tubes each. In case the tap was traumatic, the specimen was collected serially until the fluid became clear. The tubes were labelled as '1' and '2' based on their collection. The specimen was then sent to microbiology unit within 30 minutes of collection with special request form that contains demographic data, brief clinical description and whether patient has taken any prior antibiotics or not.

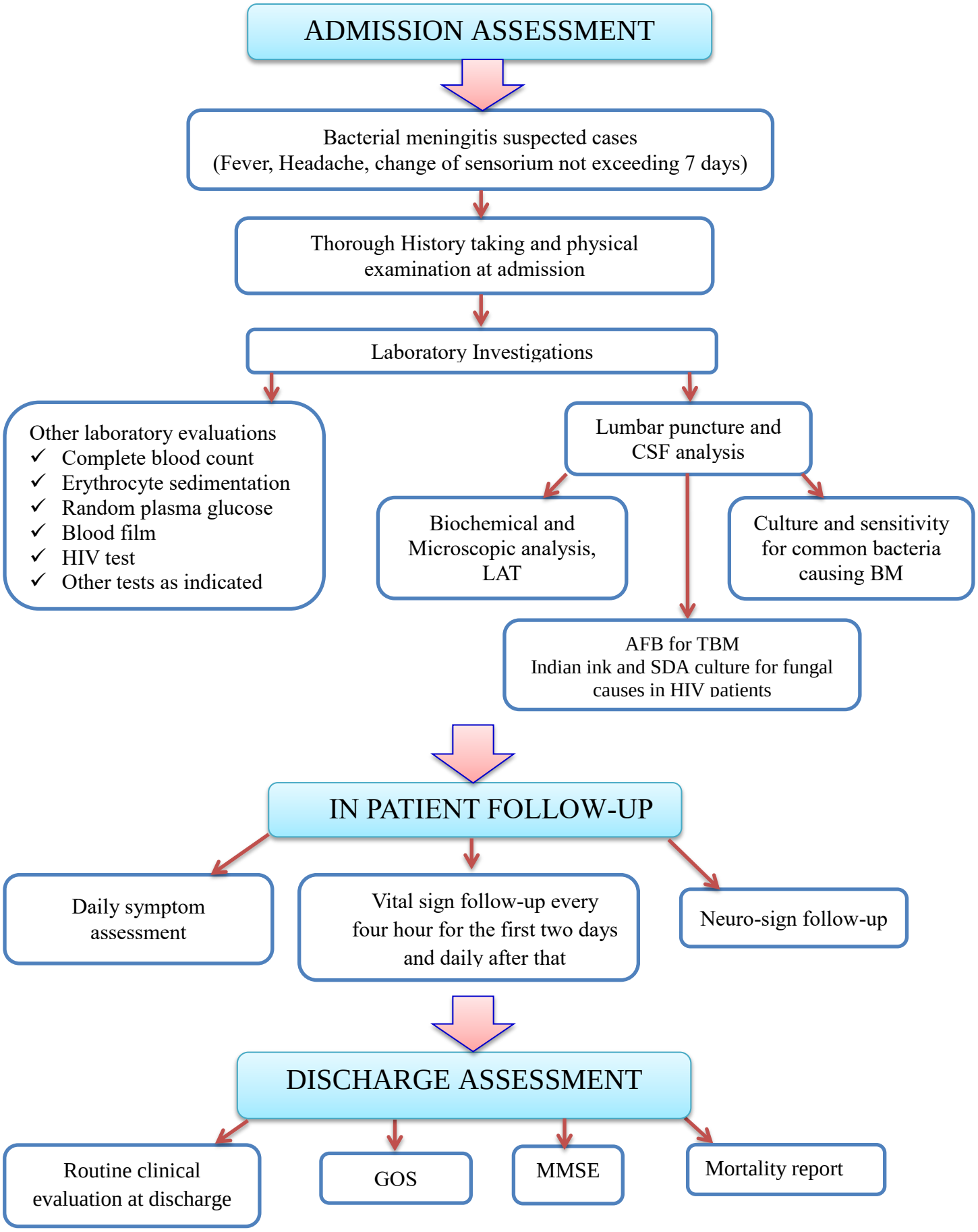


Figure 3-3 Flow chart for evaluation of patients treated as bacterial at Jimma University Specialized hospital

AFB – Acid-fast bacilli, CSF – cerebrospinal fluid, GOS – Glasgoc outcome scale, LAT – latex agglutination test, MMSE – Minimental state examination, SDA – Sabouraud's dextrose agar, TBM – Tuberculous meningitis

Samples were processed within ½ an hour to 1 hour of collection. Macroscopic appearance of CSF was observed and documented as crystal clear, turbid or bloody/traumatic by both the collecting physician and the laboratory personnel independently. Biochemical, cytological and microbiologic analysis of the specimen was done and interpreted according to guideline highlighted in **Annex – 3**.

Other laboratory tests and work-up – Plasma glucose was determined for all patients on presentation. However, only glucose level determined two hours before or after CSF collection was used for assessment of CSF to serum ratio. Complete blood count, blood film (BF) for hemoparasite and erythrocyte sedimentation rates (ESR) were done on presentation or a day after admission. Patients who were suspected to have chest infection were sent for chest radiography as soon as it was possible.

Rapid test for HIV was done within three days of admission for all patients and as soon as possible in patients suspected to have the infection. The standard confirmatory test was done for those with rapid test positive; tie-breaker test was done if there was discrepancy between the two (all done as part of routine practice). HIV test was not needed in those with known diagnosis. CD_4 count and routine evaluation for status of HIV infection (WHO staging) were done before discharge when possible. Otherwise, patients with stable conditions were discharged and given short appoint for HIV treatment (as part of routine care).

Inpatient follow-up – The course of the disease, complications, and outcome in the hospital were assessed as described below: (see **Annex – 2**)

- All treatment regimen given were documented from order sheet located in patient's chart– type, dose and route of antibiotics; adjunctive treatment (e.g., dexamethasone); treatment for additional or alternative diagnosis
- Patients were interviewed daily for symptom improvement or occurrence of new symptoms.
- Vital signs were assessed every 4 hourly for the first 48 hours and daily after that. Patients who did not show improvement in the first two days were also closely followed until improvement, death or leaving hospital.
- Daily follow-up with neurosign chart that included the following variables: Glasgow coma scale (GCS), seizure, headache, and nuchal rigidity was done during the course in hospital.

- Death occurrences were documented along with the date and possible immediate causes using separate format
- Discharge outcome was done using Glasgow outcome scale (GOS) (see below)
- Patients were also assessed at discharge for gross neurologic deficits (visual problem, hearing loss, body weakness) and minimental state examination.

Data collectors

All clinical assessments were done by medical residents directly involved in the care of patients with bacterial meningitis. Microbiologic analysis of the CSF specimen was done by laboratory professionals who received adequate (>3 months) onsite training by microbiologist from Ludwig-Maximilians University of Munich, Germany (Dr. med. Andreas Wieser). A research nurse was recruited specifically for this project to serve as a link between principal investigator, data collector physicians and laboratory personnel. He was responsible for taking collected CSF specimen to the laboratory, supervise daily in patient follow-up, collecting laboratory results and compiling of individual patient data.

The project was presented to all clinical staffs working in department of internal medicine before the commencement of data collection (February 2013). Detail data collection procedure and specimen handling was presented to all data collectors (all medical residents) after that. This was repeated at different times based on the gaps identified during data collection. All newly joining residents were also trained as required.

3.2.4. Outcome measurements

The primary outcome measurements were GOS and mortality at discharge. Neurologic deficits at discharge, length of hospital stay, and mini-mental state examination (MMSE) were the other outcome measurements.

Glasgow outcome scale (GOS) is a five-point scale described as—death=**1**, persistent vegetative state=**2**, severe disability=**3**, moderate disability=**4**, and good recovery=**5** (51). The scores were dichotomized into **favorable** (5) and **unfavourable** (1 to 4) outcomes. (See **Annex – 2**)

Mini-mental state examination (MMSE) – a 30 point score (Folstein test (52)) cognitive function assessment was done at discharge. This was used in prospective study only. Scores of 24-30 were categorized as normal. (**Annex – 2**)

Note: - MMSE was done only in patients who were conscious and were literate enough to do it.

3.3. Data quality control

The following data quality control measures were taken in both types of the studies:

- All clinical evaluations were done by clinician who had experience in care of the case.
- Data collectors were selected based on their interests only
- Data collectors were trained and data collection was supervised
- The questionnaire was pretested before data collection
- The data was double entered to minimize errors

3.4. Data processing, analysis and interpretation

The collected data were checked for completeness and consistency and then entered to EpiData version 3.1. The data were later transferred to SPSS® (IBM Corporation) version 20 for analysis. Descriptive statistical analysis was used to present sociodemographic variables, clinical and laboratory data of the patients. Trend change in disease pattern was analysed in relation to seasonal change and average annual rain fall and presented in graphs.

Chi-square test where applicable was done to test binary association between dependent and independent variables. T-test was done for continuous variables. Bivariable analysis was done to identify association between dependent and independent variables. All independent variables with $p<0.25$ in bivariate analysis were entered for multivariable analysis. Forward logistic regression analysis was done to identify the best fit model. Independent predictors were analysed for three outcome variables – death, Glasgow outcome scale and neurologic sequelae at leaving hospital. P-value of <0.05 was used as level of statistical significance.

3.5. Operational definitions

Anemia – defined as hemoglobin concentration of <12 g/dl in women and <13 g/dl for men. Hemoglobin level <8 g/dl was considered as *severe anemia*.

Antimeningeal dose of antibiotics – refers to high dose intravenous antibiotics (ceftriaxone 2gm every 12 hours, ampicillin 3gm every 6 hours, benzyl penicillin 4 million units every 4 hours).

Level of consciousness – was assessed using Glasgow Coma Scale (GCS) which has a score of 3 to 15. Full consciousness refers to score of 15; a score of 9-14 was considered as *impaired consciousness* and patients with a score of 8 or less were classified as comatose.

Neurologic deficit refers to (1) unilateral extremity weakness [monoparesis or hemiparesis] (2) unilateral loss of sensation (3) localized cranial nerve palsies (III, IV and VII).

3.6. Ethical considerations

The study was approved by College of Health Science Ethical Review Board at Jimma University (Reference letters **RPGC/24/2013** and **RPGC/4026/2015**). Official letter was then written by the review board to each respective hospital to facilitate access to the archives. Written informed consent was obtained from patients or close family member if the patient was uncommunicative (for prospective study). Culture findings and antibiotic susceptibility test results were communicated to the treating physicians as soon as the results were known. Physicians at the hospitals were informed about the findings to make use of them in patient care. Data was collected using medical registration number and patients initials only. Confidentiality of the data was ensured through anonymity.

4. Results

4.1. Retrospective study

Background characteristics – A total of 425 patients treated for suspected bacterial meningitis at four teaching hospitals in Ethiopia were included in this study; 224 (52.7%) of them were male. The mean age at presentation was 32 years (SD = 15.7) with a range of 14 to 85 years; 356 (83.8%) were younger than 50 (**Table 4.1**).

Table 4-1 – Background characteristics of patients treated as bacterial meningitis at teaching hospitals in Ethiopia, 2011 – 2015.

Characteristics	Number	Percent
Gender		
Male	224	52.7
Female	201	47.3
Age at presentation		
< 50 years	356	83.8
≥ 50 years	69	16.2
Duration of illness before presentation		
0-2 days	127	29.9
3-7 days	234	55.1
>7 days	64	15.1
Presenting symptoms and signs		
Fever	384	90.4
Headache	359	84.5
Nuchal rigidity	238	56.0
Vomiting	243	57.2
Loss of consciousness	213	50.1
Seizure	98	23.1
Photophobia	42	9.9
Focal neurologic deficit	33	7.8
Prior antibiotic treatment	104	24.5
Hospital		
Arba Minch	126	29.6
Gondar	92	21.6
Hawassa	85	20.0
Jimma	122	28.2
Risk factors/comorbidities identified		
HIV	23	5.4
Pregnancy	14	3.3
Diabetes mellitus	8	1.9
Current alcohol user	7	1.6
Current smoker	3	0.7
Acute otitis media	2	0.5
Chronic otitis media	1	0.2
Head injury and CSF leak	2	0.4

Presenting clinical symptoms: Fever, headache and neck stiffness were the most common presenting symptoms reported in 384 (90.4%), 359 (84.5%) and 238 (56 %) of cases, respectively. At presentation to the emergency unit, 213 (50.1% had impaired consciousness (GCS<15) and 7.8% had focal neurologic deficit.

On average, the duration of illness before presentation was 5.1 days (SD=4.3). About 85% of patients presented within a week of onset of symptoms. However, only 79 (18.6%) patients presented within a day after symptoms had begun. Nearly quarter of the patients (104) were treated in the community with antibiotics for similar complaints. HIV infection and diabetes mellitus were the most common comorbidities identified and were reported in 5.4% and 1.9% of cases respectively (**Table 4.1**). However, the diagnosis of diabetes was self-report and 17.9% of patients did not receive HIV test. Thus, the report of these comorbidities may be an under estimate of the real prevalence.

Table 4-2 – Diagnostic and ancillary laboratory investigations done in patients treated as bacterial meningitis at teaching hospitals in Ethiopia, 2011 – 2015.

Type of laboratory tests	Number	Percent
Lumbar puncture done	236	55.5
Reasons documented for not doing LP (N=189)		
Contraindications	49	25.9
Technical problem (failed attempt)	9	4.8
No LP set	2	1
Not known	126	66.7
CSF analysis (N=236)		
Glucose	165	69.9
Protein	137	58.1
Cell count	180	76.3
Gram stain (microscopy)	220	93.2
Culture	61	25.8
AFB test	208	88.1
Indian ink for Cryptococcus	80	33.9
Other supportive tests (N=425)		
Complete blood count	335	78.8
Erythrocyte sedimentation rate	156	36.7
Blood glucose	246	57.9
HIV test	349	82.1
Blood film for hemoparasite	397	93.4

LP – lumbar puncture, AFB – acid fast bacilli

Diagnostic strategies – Only 236 (55.5%) of patients had a lumbar puncture done to collect CSF specimen. Among them, 220 (93.2%) had microscopic examination of Gram-stain specimen for causative bacteria and 180 (76.3%) had leukocyte count done. However, only 58.1% had analysis for both protein and glucose. Culture and antibiotic sensitivity tests were

done in only 61(25.8%) cases (**Table 4.2**). A pathogen was identified in only 14 cases (6%) of those who had their CSF collected. Blood culture was not done in any of the patients.

Findings from CSF analysis showed that only less than half of the patients had one or more of the following abnormalities considered as compatible with bacterial meningitis – CSF/serum glucose ratio < 0.4 or WBC ≥ 100cells/mm^3 or protein >100mg/dl (**Table 4.3**). Causative bacteria were detected by microscopic examination of CSF specimen in only 13 cases; seven of them were reported as gram-negative intracellular diplococcus (*Neisseria meningitidis*) whereas six were reported as extracellular gram-positive diplococcus (*Streptococcus pneumoniae*). Only one of these cases was positive on culture. In another case with negative gram-stain finding, culture was found to be positive for *Streptococcus pnuemoniae*. One patient who was also positive for HIV had confirmed cryptococcal meningitis.

In other supportive tests, 38% had peripheral leucocytosis and 4% were severely anaemic. Twenty-eight patients had positive blood film for plasmodium species (**Table 4.3**).

Table 4-3 – Supportive laboratory findings for diagnosis of bacterial meningitis in patients treated as bacterial meningitis at teaching hospitals in Ethiopia, 2011 – 2015.

Laboratory findings	Number	Percent
CSF analysis		
Turbid/cloudy CSF (of 235 cases)	57	24.3
CSF glucose (of 111 tested)		
CSF/serum ratio <0.4	47	42.3
White cell count (of 180 tested)		
>10 cells/mm^3	116	64.4
>100 cells/mm^3	81	45.0
>1000 cells/mm^3	34	18.9
Protein (of 140 tested)		
>50 mg/dl	83	59.3
>100 mg/dl	59	42.1
Organism detected by microscopic examination of CSF (of 220 tested)	13	5.9
Positive culture (of 61 tested)	2	3.3
Complete blood count (total = 335)		
Leukopenia (<4000/µl)	33	9.9
Leucocytosis (>11,000/µl)	127	37.9
Anemia	105	31.3
Severe anemia	13	3.9
Blood film Positive for malaria (T=397)	28	7.1

Overall, the diagnosis of bacterial meningitis was microbiologically confirmed in only 14 (3.3%) cases whereas additional 82 (19.3%) cases had CSF abnormalities compatible with bacterial meningitis (*possible bacterial meningitis*). Another, 196 (46.1%) patients fulfilled

the World Health Organization (WHO) criteria for clinical *suspected unproven* cases of bacterial meningitis. The rest, 133 (31.3%) did not fulfil both clinical and laboratory criteria for definition of bacterial meningitis (*non-cases*). On further analysis, 82 (41.8%) of suspected unproven cases and 58 (43.6%) of the non-cases had at least partial analysis of their CSF. None of these groups had findings that supported the diagnosis of bacterial meningitis but they continued to receive antibiotics as so.

In general, of the 236 patients who had their CSF analysed, only 96 (40.7%) had findings compatible with diagnosis of bacterial meningitis. This means, among all patients treated as bacterial meningitis; only 22.6% (96/425) were supported by CSF findings (**Figure 4.1**).

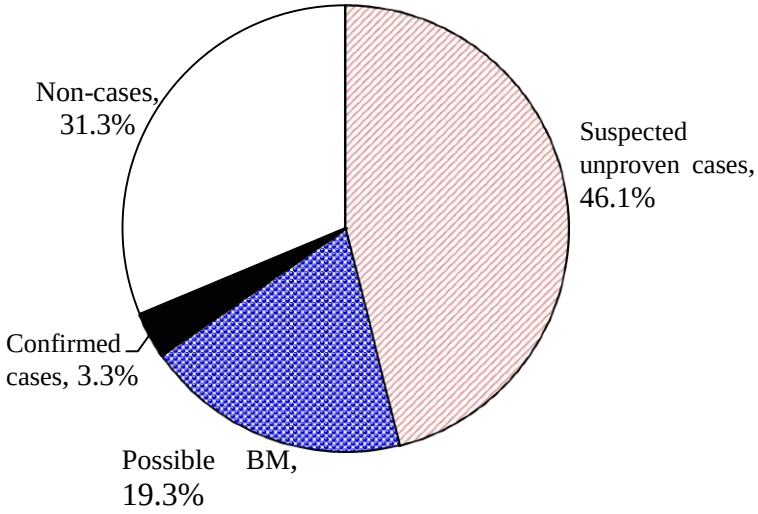


Figure 4-1– Classification of the cases based on WHO case definition for bacterial meningitis in patients treated as bacterial meningitis (BM) at teaching hospitals in Ethiopia, 2011 – 2015.

Treatment strategies

Antibiotic choice: All of the patients were given antimeningeal dose of intravenous antibiotics until death, hospital discharge or for at least 10 days in case patient stayed in hospital for other reasons. Except for one patient, all of them took ceftriaxone either as a single agent or in combination with other antibiotics; 75 (17.6%) were given vancomycin and 23 (5.4%) took ampicillin as additional treatment. Intravenous metronidazole was given to 44 (10.4%) patients for suspected aspiration pneumonia.

We have also tried to assess if selection of antibiotics used was based on clinical profiles of the patients. This analysis showed that there was no difference in vancomycin use among age

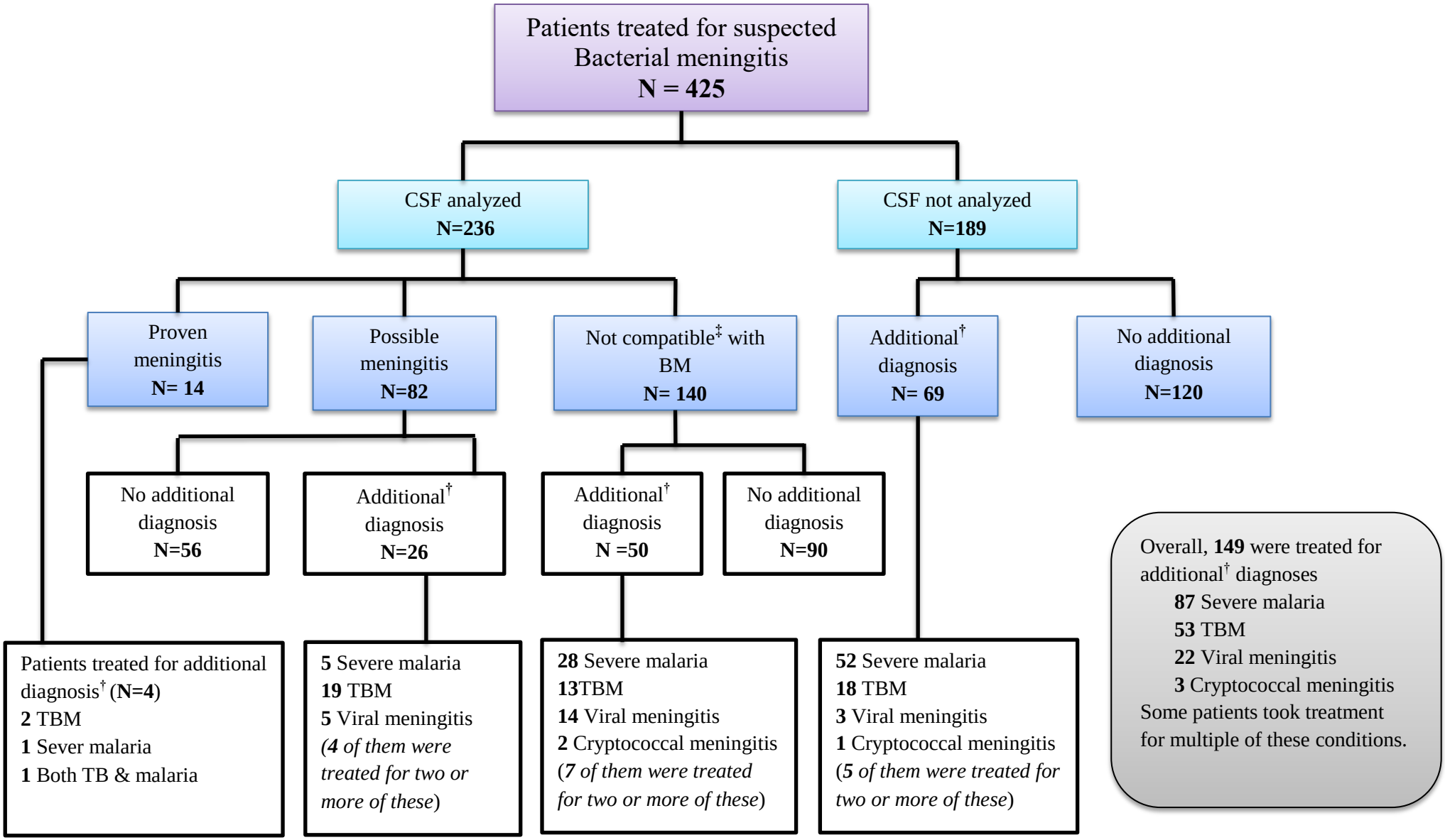
groups and clinical conditions of the patients. On the other hand, it was found that ampicillin was administered more often in pregnant woman, 85.7% vs 5.1% in non-pregnant (P<0.001) and those older than 50 years of age (26.1% vs 1.4% in younger patients (P<0.001)).

Antibiotic choices and duration of therapy for BM did not significantly vary with clinical scenario of the patient and CSF findings. However, variations were observed between hospitals and even within each hospital.

Concomitant treatment for additional etiology: As stated above, etiologic diagnosis was not possible from CSF for most of the patients. Hence, physicians took pragmatic approach of treating these patients for other differential diagnoses. Accordingly, 149 (35.1%) patients were treated for one or more of these additional diagnoses (Tuberculous meningitis, viral meningitis, cryptococcal meningitis and severe malaria). Eighty-seven (20.5%) were given antimalarial treatment, however, only 28 (32.2%) of them were confirmed by blood film and only 19 were having *Plasmodium falciparum*. Anti-tuberculous treatment was given empirically for 53 (12.5%) though they were not confirmed by laboratory. Twenty-two patients were also treated with high dose oral acyclovir when viral meningitis seemed also possible on clinical ground. All of these patients treated for alternative/additional diagnosis were also given full antibiotic regimen for BM. **Figure 4.2** summarizes diagnostic and therapeutic flow chart employed for overall management of the cases.

As the cases treated for TB meningitis and viral meningitis were not confirmed by laboratory, we tried to assess if these patients were clinically different from the other groups. In this regard, patients treated as TB meningitis were those who had longer duration of illness before presentation, 8.8 versus 4.7 days (P<0.001); had prior antibiotic treatment before hospital presentation, 18.3% versus 10.6% (p=0.04) and had focal neurologic deficit, 27.3% versus 11.3% (p=0.008). However, patients treated as viral meningitis had similar clinical profile as others except that they had higher rate of seizure, 10.2% versus 3.7% (p=0.01) and loss of consciousness, 8.1% versus 2.8% (p=0.024).

Adjunctive dexamethasone treatment: Adjuvant dexamethasone was given to 214 (50.4%) of patients. It was used in 85.7% of proven, 62.2% of possible and 42.9% of suspected BM. It was also used in 57.7% of patients who did not have CSF analysis. Moreover, 52.3% patients treated for additional etiologies were also given this adjuvant therapy.



‡ CSF was only partially analysed for 42.7% of the cases; not enough to completely rule out bacterial meningitis

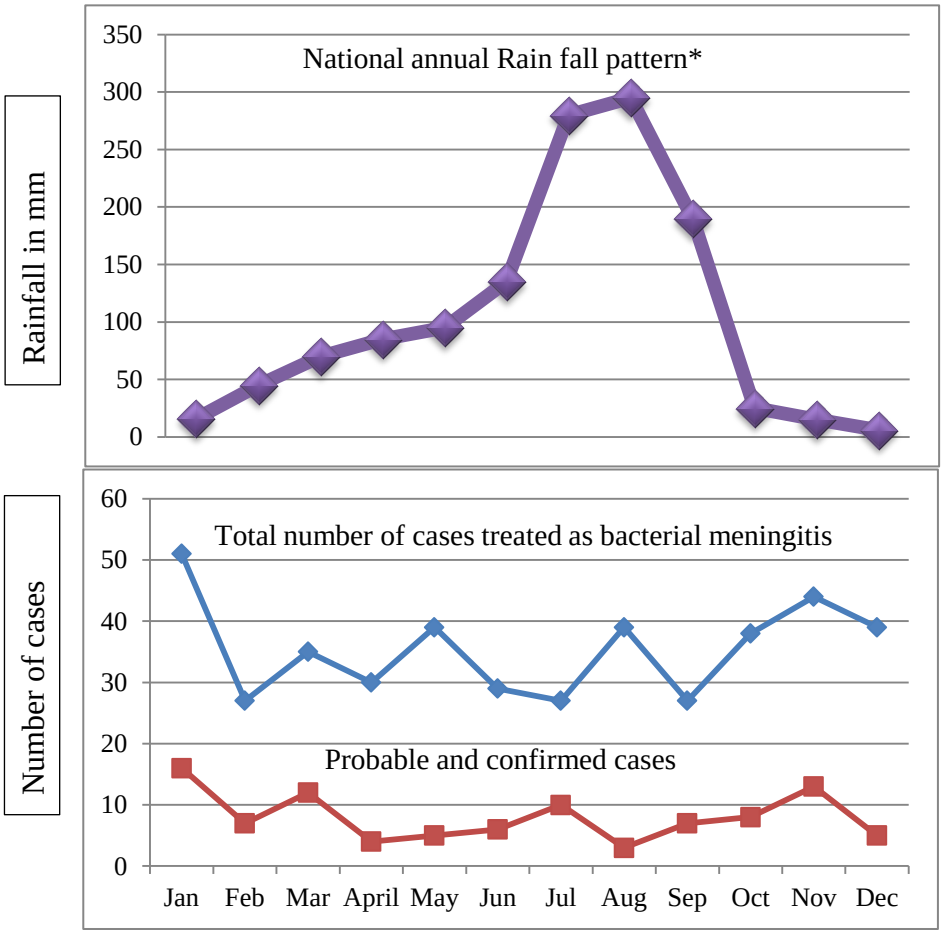
† None of the TBM (Tuberculous meningitis) and viral meningitis cases were confirmed microbiologically, only 1 of the cryptococcal meningitis cases and 28 of malaria cases were confirmed. Treatment was thus mostly empiric.

All 425 patients took full regimen of antibiotics for bacterial meningitis (BM).

Figure 4-2– Classification of cases treated as bacterial meningitis based on diagnosis and treatment approach used at teaching hospitals in Ethiopia, 2011 – 2015.

Seasonality of the disease occurrence

Trend change in number cases was analysed in relation to the amount of average annual rainfall pattern. There was no smooth variation of number of cases in relation to the amount of rainfall. However, the peak number of cases between November and January correlates well with the lowest annual rainfall. On more specific analysis for probable and confirmed cases of bacterial meningitis, the peak was in dry month of January whereas the nadir was registered in August, the month with highest rainfall (**Figure 4.3**).



**Data extracted from National Metrology Agency (http://www.ethiomet.gov.et/)*

Figure 4-3 – Seasonal variability of number of cases treated as bacterial meningitis with rainfall pattern

In terms of yearly change, 321 (75.5%) of patients were treated in the year 2013 and 2014. Whether the steady increment from 2011 and 2012 was due to change in pattern or lost documents in the earlier year is not clearly know though the latter is most likely explanation. The seasonal variation in each year also

lacks clear pattern but, the number of reported cases were found to be highest between December and February (the driest months of the year) each year except for 2014 (**Figure 4.4**).

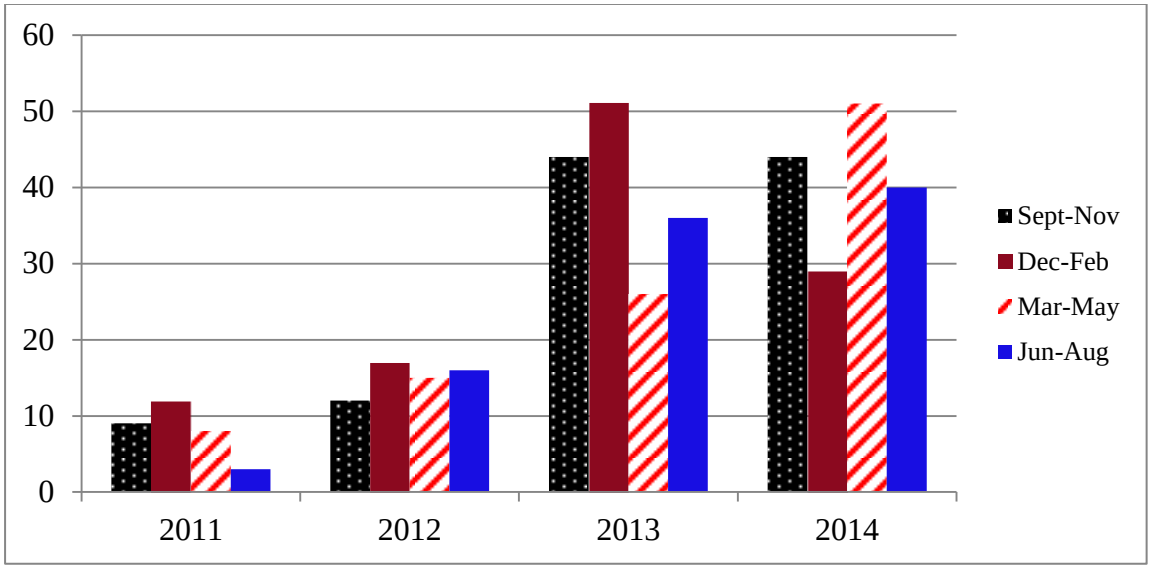


Figure 4-4 – Number of cases treated as bacterial meningitis by season and year at teaching hospitals in Ethiopia

Discharge outcome – 156 (36.7%) had unfavorable outcome (GOS = 1-4) at leaving hospital. The overall in hospital mortality rate was 20.2% (86 deaths). There were differences in mortality rates based on case definition of bacterial meningitis; 26.0% in suspected unproven cases, 20.7% in possible bacterial meningitis, 28.6% in confirmed cases and 10.5% in non-cases (P<0.0001).

The median time from hospital admission to death was 3 days; 55.8% happened in the first 4 days after admission.

Of those who left the hospital alive (339), 277 (81.7%) were discharged and 57 (16.8%) left against medical advice (LAMA). Among surviving patients, 70 (20.6%) had unfavourable GOS (2 to 4); 38 (11.2%) had documented neurologic sequelae.

The average length of hospital stay (LOS) for discharged patients was 11.0 days (SD=6.6). Those who left against medical advice had a LOS of 6.1 days (SD=3.7) and 52.6% of them left in the first 4 days of admission (**Table 4.4**).

Table 4-4 – Outcome at leaving hospital in patients treated as bacterial meningitis at teaching hospitals in Ethiopia, 2011 – 2015.

Characteristics	Number	Percent
Status at leaving hospital (N=425), n (%)		
Discharged	277	65.2
Left against medical advice	57	13.4
Referred	5	1.2
Died	86	20.2
Discharge condition of survivors (N=339), n (%)		
Complete recovery	230	67.9
Some improvement	78	23.0
The same as admission	31	9.1
GOS (N=425), n (%)		
1	86	20.2
2	22	5.2
3	9	2.1
4	39	9.2
5	269	63.3
Neurologic sequelae (N=38*), n (%)		
Low GCS	18	47.4
Neurologic deficit	11	28.9
Seizure	9	23.7
Cranial nerve palsy	2	5.3
Length of hospital stay in days	**Mean**	**SD**
Total	8.9	6.4
Discharged patients	11.0	6.6
LAMA	6.1	3.7
Referred	7.4	5.2
Died	4.0	3.4

*2 Patients had multiple complications

GOS – Glasgow outcome scale, LAMA – left against medical advice

Predictors of poor outcome –*In hospital death* – Admission Glasgow coma scale, presence of pneumonia and cranial nerve palsy during hospitalization, and treatment with dexamethasone were found to be independently associated with increased mortality. Accordingly, low GCS (impaired consciousness) was associated with poor outcome and improvement of GCS by 1 was associated with an increment of survival chance by 21% (AOR = 0.79; 95% CI = 0.73 – 0.85). Patients who had pneumonia at presentation were three times more likely to die in hospital than patients without pneumonia (AOR = 2.97; 95% CI= 1.38 – 6.41). Similarly, presence of cranial nerve deficits (III, VI and VII) at admission was associated with nearly 5 times increment of mortality (AOR = 4.73; 95% CI = 1.45 – 15.50). Adjunctive dexamethasone treatment was also associated with over 3 times increment of mortality (AOR = 3.38; 95% CI = 1.87 – 6.12) (**Table 4.5**).

Glasgow outcome scale (GOS) was dichotomized into favorable (GOS = 5) and unfavorable (GOS =1 to 4) outcome. Low admission GCS (AOR = 0.77; 95% CI = 0.66 – 0.89) and dexamethasone treatment (AOR = 4.46; 95% CI 1.98 –10.08) were again found to be independently associated with unfavorable outcome at discharge.

Fifty-two (12.2%) of patients were additionally treated with anti-tuberculous drugs with the presumptive diagnosis of tuberculous meningitis (TBM). These groups of patients had unfavourable outcome at discharge as compared to other groups (AOR = 2.78; 95% CI 1.06 – 7.30).

Neurologic sequelae – Focal neurologic deficits (AOR = 3.33; 95% CI 1.31 – 8.50), seizures (AOR = 2.20; 95% CI 1.03 – 4.67) and a low level of consciousness (AOR = 2.65; 95% 1.21 – 5.81) at admission were associated with the occurrence of neurologic sequelae at discharge. The duration of illness before presentation was also associated with an increased occurrence of neurologic complications at discharge (AOR = 1.09; 95% CI 1.01 – 1.16). Accordingly, likelihood of this complication was found be increased by 9% for each day between onset of symptoms and presentation to the hospital.

Table 4-5 – Factors independently associated with poor outcomes at leaving hospital in patients treated as bacterial meningitis at teaching hospitals in Ethiopia, 2011 – 2015.

Variable	AOR	95.0% C.I.	P-value
Death			
Level of consciousness at presentation (*for a point increase in GCS*)	0.79	0.73 – 0.85	<0.001
Dexamethasone treatment	3.38	1.87 – 6.12	<0.001
Aspiration pneumonia at presentation	2.97	1.36 – 6.41	0.006
Cranial nerve palsy at presentation	4.73	1.45 – 15.50	0.010
Low GOS			
Level of consciousness at presentation (*for a point increase in GCS*)	0.77	0.66 – 0.89	<0.001
Dexamethasone treatment	4.46	1.98 – 10.08	<0.001
TB suspected cases	2.78	1.06 – 7.30	0.038
Neurologic sequelae			
Focal neurologic deficit at presentation	3.33	1.31 – 8.50	0.012
Seizure at presentation	2.20	1.03 – 4.67	0.041
Duration of illness before presentation in days	1.09	1.01 – 1.16	0.020
Impaired consciousness	2.65	1.21 – 5.81	0.015

As described above, 15% of patients left hospital against medical advice or referred for better care. Separate analysis was done to assess if these patients differed clinically from discharged patients. Accordingly, they were found to have lower GOS, lower GCS and higher proportion of neurologic sequelae at leaving hospital (**Table 4.6**).

Table 4-6 – Difference in secondary outcome variables between discharge patients and those who left the hospital against medical advice or referred to other centres in patients treated as bacterial meningitis at teaching hospitals in Ethiopia, 2011 – 2015.

Discharge outcome	**GOS, N (%)**					**Neurologic sequelae, N (%)**			**Impaired GCS, N (%)**		
	2	3	4	5	P	Yes	No	P	Yes	No	P
LAMA/referred	21 (33.9)	6 (9.7)	20 (32.3)	15 (24.2)	<0.001	16 (25.8)	46 (74.2)	<0.001	13 (21.0)	49 (79.0)	<0.001
Discharged	1 (0.4)	3 (1.1)	19 (6.9)	254 (91.7)		18 (6.5)	259 (93.5)		2 (0.7)	275 (99.3)	

Dexamethasone treatment and its association with discharge outcomes – Chi-square test showed that dexamethasone was used more often in confirmed and probable cases of bacterial meningitis, those with turbid CSF and organism detected by Gram staining. On the other hand, it was found to be prescribed less often in HIV-positive patients as compared to non-HIV cases. There was also a clear difference in the pattern of dexamethasone treatment between hospitals ranging from 23.5% in Hawassa to 73.9% in Gondar. However, there was no difference with respect to presenting clinical conditions and prior antibiotic treatment (**Table 4.7**).

Table 4-7 – Comparison of background characteristics by dexamethasone treatment of patients treated as bacterial meningitis in Ethiopia, 2011 – 2015.

Characteristics	Dexamethasone	No dexamethasone	P value
Mean age, year (SD)	30.1 (15.0)	33.9 (16.2)	0.116
Duration of illness, days (SD)	5.2 (4.3)	5.0 (4.3)	0.683
Diagnosis of meningitis			
Confirmed	12 (85.7)	2 (14.3)	0.001*
Probable	51 (62.2)	31 (37.8)	
Suspected	84 (42.9)	112 (57.1)	
Non-cases	67 (50.4)	66 (49.6)	
Prior antibiotic treatment			0.096
Yes	45 (43.3)	59 (56.7)	
No	169 (52.6)	152 (47.4)	
Impairment of consciousness			0.52
Yes	102 (52.0)	94 (48)	
No	112 (48.9)	117 (51.1)	
Focal neurologic deficit			0.051
Yes	22 (66.7)	11 (33.3)	
No	192 (49.0)	200 (51.0)	
CSF appearance			<0.001*
Turbid	37 (64.9)	20 (35.1)	
Normal	68 (38.2)	110 (61.8)	
Detection of organism by Gram stain			0.003*
Yes	11 (84.6)	2 (15.4)	
No	89 ((43.0)	118 (57.0)	
HIV status			0.048*
Positive	7 (30.4)	16 (69.6)	
Negative	207 (51.6)	194 (48.4)	
Hospital			<0.001
Jimma	52 (42.6)	70 (57.4)	
Gondar	24 (26.1)	68 (73.9)	
Hawassa	65 (76.5)	20 (23.5)	
Arba Minch	73 (57.9)	53 (42.1)	

**statistically significant*

Dexamethasone treatment was associated with an increase of the in-hospital mortality, COR = 3.18 (95% CI 1.90-5.33); p<0.001 and low GOS at discharge, COR = 2.65 (95%CI 1.76-3.99); P < 0.001. Multivariate logistic regression analysis also showed that dexamethasone treatment was independently associated with an increased in hospital mortality, AOR = 3.38 (95% CI 1.87-6.12); P < 0.001 and unfavorable overall outcome, AOR = 4.46 (95%CI 1.98-10.08); P < 0.001. However, there was no association with neurologic sequelae at discharge (**Figure 1**).

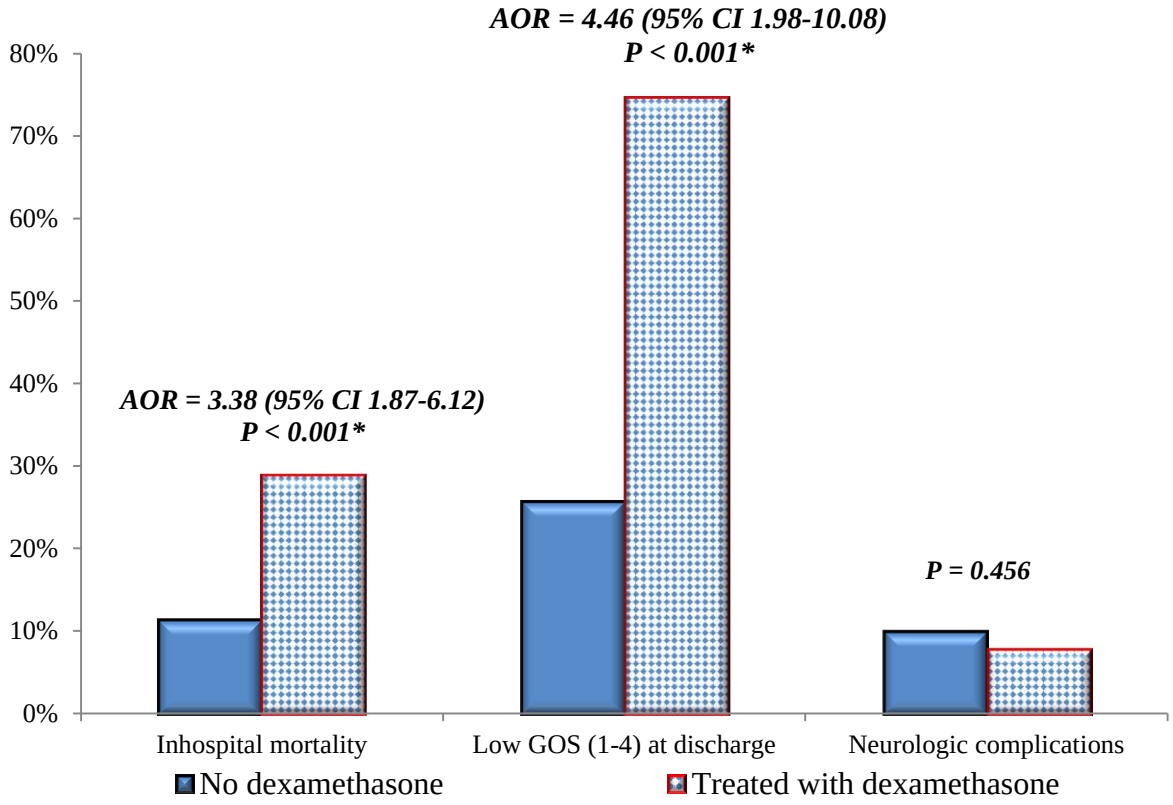


Figure 4-5 – Effect of adjuvant dexamethasone treatment on discharge outcome in patients treated as bacterial meningitis in Ethiopia, 2011 – 2015.
GOS – Glasgow Outcome Score

As depicted on **Table 4.5** above, dexamethasone was found to be one of the factors independently associated with poor outcome on multivariable analysis with best-fit model. When further analysis was done controlling for all potential confounders on multiple logistic regressions with forced entry, this association persisted. For instance, the odds of having low GOS at discharge was nearly 4 times, AOR=3.94 (95%CI 1.63-9.53; P=0.002) and its association with in hospital death was also nearly as much, AOR= 3.60 (1.97-6.60; P<0.001).

Controlling for these individual variables also revealed similar finding as shown on **Table 4.8**.

Dexamethasone and mortality – This association did not differ between older and younger patients, whether patient had delayed presentation or not, and whether patient took prior antibiotic or not. However, this association faded in HIV infected patients, those with neurologic deficit on presentation, those with abnormal CSF findings, and TB suspected cases.

Dexamethasone and low GOS – Age of the patient, presence or absence of HIV infection, and prior antibiotic treatment did not change the nature of this association. On the other hand, the association disappeared in TB suspected cases, those with confirmed BM and neurologic deficit on presentation.

Table 4-8 – Relationship between dexamethasone and discharge outcome after controlling for potential confound variables

Variables	Death			Low GCS		
	OR	**95% CI**	**P**	**AOR**	**95% CI**	**P**
Age						
< 50 years	3.08	1.74-5.48	<0.001*	2.83	1.79-4.48	<0.001*
≥ 50 years	4.00	1.19-13.46	0.025*	2.68	1.0-7.21	0.051
Duration of illness						
≤ 2 days	4.02	1.37-11.77	0.011*	2.05	0.94-4.50	0.072
> 2days	2.93	1.62-5.30	<0.000*	2.91	1.79-4.72	<0.001*
Level of conscious						
Conscious (GCS=15)	3.19	0.97-10.52	0.057	1.92	0.95-3.89	0.069
Impaired (GCS=3-14)	3.04	1.65-5.61	<0.001*	3.17	1.81-5.57	<0.001*
HIV status						
Positive	3.25	0.46-22.93	0.237	18.00	1.63-198.51	0.018*
Negative	3.38	1.91-5.66	<0.001*	2.49	1.63-3.80	<0.001*
Prior antibiotics						
Yes	3.59	1.24-10.38	0.018*	5.97	2.47-14.44	<0.001*
No	3.04	1.68-5.50	<0.001*	2.07	1.30-3.29	0.002*
Focal neurologic deficit						
Yes	3.20	0.67-15.38	0.146	0.80	0.16-3.99	0.789
No	3.00	1.72-5.23	<0.001*	2.77	1.80-4.29	0.003*
CSF appearance						
Turbid	2.72	0.67-11.11	0.163	2.44	0.79-7.51	0.121
Clear	6.26	1.95-20.12	0.002*	4.28	2.14-8.58	<0.001*
TB suspected						
Yes	3.90	0.45-34.02	0.218	3.46	0.83-14.36	0.087
No	3.09	1.79-5.34	<0.001*	2.18	1.40-3.39	0.001*
Diagnosis of meningitis						
Confirmed	-	1	1	-	1	1
Probable	2.31	0.68-7.86	0.180	3.22	1.24-8.36	0.016*
Suspected	3.38	1.73-6.59	<0.001*	2.09	1.16-3.75	0.014*
Non-cases	6.98	1.50-32.56	0.013*	3.17	1.41-7.15	0.005*

**statistically significant*

In summary, adjunctive dexamethasone treatment was associated with poor outcome in most of the groups except for patients whose diagnosis of bacterial meningitis is more likely as evidenced by turbid CSF and confirmed etiology, and in those suspected to have TBM. In these cases, dexamethasone therapy was not associated with any positive or negative discharge outcomes (**Table 4.8**).

One instance where dexamethasone with associated with positive outcome is decreased discharge neurologic sequelae in patients who had impaired consciousness at presentation, AOR=0.42 (95% CI 0.19-0.94; P=0.033).

Key findings from retrospective study (summary)

Total of 425 participants, 83.8% of which were younger than 50, were included in the study. Fever and headache were major presenting symptoms and half of them presented with impairment of mentation. Only 30% of patients presented within 2 days of symptom onset. A quarter of them took antibiotic therapy in the community for the same complaint before hospital presentation. The peak number of cases treated as BM at the hospitals correlates with lowest annual rain fall (November to January).

Lumbar puncture for CSF collection was done in only 55.5% of patients and only 58% of them had complete biochemical and cytological analysis of the CSF. CSF abnormality compatible with BM was documented in only 96 patients and a pathogen was detected in 14 cases only.

Eighty-six patients (20.2%) died before leaving hospital. Mortality was found to be high in those admitted with impaired consciousness, cranial nerve palsy and comorbid pneumonia. Adjunctive dexamethasone treatment was used in 50.4% of cases and was independently associated with increased in hospital death (AOR=3.38, 95%CI =1.87-6.12) and low GOS (AOR=4.46, 95%CI=1.98-10.08).

4.2. Prospective study

Study participants (Baseline characteristics)

Total of 127 patients were included in this study. The mean age of the participants was 32.7 years (SD=13.1) with range of 18 to 70; 108 (85%) were younger than 50. Men constituted for the majority, 79 (62.2%) of the participants. Seventy-seven (60.6%) of them were rural residents.

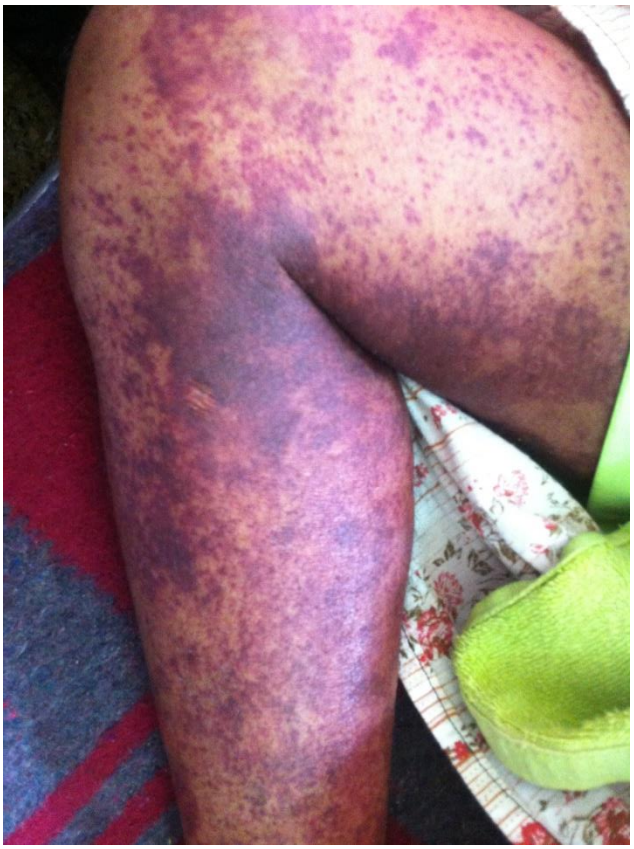
Table 4-9 – Baseline demographic and clinical characteristics of patients treated as bacterial meningitis at Jimma University Specialized Hospital, Ethiopia

Characteristics	Number	Percent
Age (years)		
<50	108	85.0
≥50	19	15.0
Gender		
Male	79	62.2
Female	48	37.8
Residence		
Rural	77	60.6
Urban	50	69.4
Duration of illness in days, mean (SD)	5.6 (4.7)	
Presenting signs and symptoms		
Fever	116	91.3
Headache	122	96.1
Nuchal rigidity	106	84.1
Vomiting	91	71.7
Impaired consciousness	64	50.4
Photophobia	52	41.3
Seizure	28	22.0
Neurologic weakness	9	7.1
Hypotension	8	6.3
Prior antibiotics	44	34.6
Route of prior antibiotics		
Oral	17	38.6
Parenteral (Intravenous or intramuscular)	27	61.4
Reported prior meningococcal vaccine	7	5.5
Known contact with patient of similar illness	3	2.4
Comorbidities		
HIV	23	18.1
Pneumonia	23	18.1
Diabetes mellitus	4	3.1
Current alcohol use	11	8.7
Current smoker	9	7.1
Others	8	6.3

The duration of illness before presentation was 5.6 days (SD=4.7) with range of 6 hours to 21 days. About 80% (101) of patients presented within seven days of symptom onset, however, only 37 (29.1%) of them presented within 2 days. Fever, headache and nuchal rigidity were the major clinical presentations reported in 116 (91.3%), 122 (96.1%) and 106 (84.1%) of the participants. Half (64) of them had impaired consciousness at presentation (**Table 4.9**).

All patients were screened for HIV using rapid diagnostic test and the rate of HIV infection was found to be 18.1% (23 cases). Among the HIV patients, 20 have been diagnosed prior to current presentation. Twenty-three (18.1%) had concomitant pneumonia which was evidenced by physical examination and chest radiography. Eleven patients (8.7%) reported regular use of alcohol and 9 (7.1) were current smokers. Six of reproductive age women were pregnant. Seven patients reported taking meningococcal vaccine recently (**Table 4.9**).

Six patients presented with petechial rashes. **Figure 4.6** presents one of those patients with BM presenting with typical petechial rash along with other clinical characteristics. This is a 70 year old man presented with sudden onset of high grade fever and intense global headache followed by skin rash over his legs within one day. On examination, he had an overwhelming non-blanching rash over his lower extremities which have become ecchymosed in some areas. His CSF was frank pus on collection and revealed an extremely high white count (76, 500 cells/μL). Patient's condition deteriorated fast despite high dose intravenous ceftriaxone. His blood pressure became unrecordable despite intravenous fluid administration. He finally died of septic shock with multisystem organ failure within 12 hours of hospital admission.



Clinical description of the patient
70 years old man
Presented on 25th of July, 2015
Duration of illness – 48 hours
GCS = 12/15
CSF findings:
- ✓ Glucose ratio = 0.4
- ✓ Protein = 198mg/dl
- ✓ White cells = 76,500 cells/μL (PMN=72%)
- ✓ CSF gram stain – negative
- ✓ LAT – positive on *N meningitidis* ACY W135
- ✓ Culture – *N meningitidis*

CBC
WBC =16,400 (PMN=73.6%)
Hb = 14.9 g/dL
Platelet =280,000/μL
Outcome – died next day of septic shock with multisystem organ failure

Figure 4-6 – Petechial rash of meningococcal meningitis with meningococcemia

CSF characteristics

Lumbar puncture to collect cerebrospinal fluid specimen was done in 109 (85.8%) of patients. In thirteen patients, LP was deferred due to contraindications (deep coma with GCS of ≤5 or focal neurologic deficit or cranial nerve palsy). In remaining 5 patients, the attempt to collect CSF specimen failed due to technical reasons. Of those who had CSF analysis, the specimen was collected after at least the first dose of antibiotics in 56 (51.4%) of patients; 21 (19.3%) had taken antibiotics for at least 24 hours (**Table 4.10**).

In 57 (52.8%) them, purulent CSF was collected of which 52 were visibly turbid. The median white cell count was 115 cells/μL with range of 0 to 76, 500 cells/μL; 41 (37.6%) patients had ≥1000 White cells/ μL. The case with highest white cell count is highlighted on **Figure 4.6**.The mean CSF protein was 114mg/dL (SD=97). Forty-seven (43.1%) had CSF to serum glucose ratio of <0.4. CSF analysis in 22 (20.2%) patients revealed normal protein concentration, glucose

level and white blood cell count (<5 cells/μL). Of these groups, 8 had microbiologically confirmed etiology (fungal and bacterial) and 14 had negative findings (**Table 4.10**).

Table 4-10 – CSF profile of patients treated as bacterial meningitis at Jimma University Specialized Hospital, Ethiopia

CSF profile	Number	Percent
Lumbar puncture done	109	85.2
Reason for not doing LP (N=18)		
Contraindication	13	72.2
Technical difficulty (failed attempt, traumatic tap)	5	27.8
Initial antibiotics before LP (of 109 tested)	56	51.4
Gross appearance of CSF (N=109)		
Turbid	54	49.5
Crystal clear	55	50.5
CSF glucose ratio (N=89)		
<0.4	47	52.8
≥0.4	42	47.2
CSF protein (N=95)		
>100	39	41.1
50-100	25	26.3
<50	31	32.6
CSF white cell (N=109)		
<100	47	43.1
100-999	21	19.3
≥1000	41	37.6
Proportion of PMN in CSF (n=109)		
≥65%	53	48.6
<65%	56	51.4
Bacteria identified by (N=26)		
Gram stain	23	88.5
LAT	15	57.7
Culture	14	51.9
At least two of them	15	57.7
All of them	8	30.8
Type of bacteria (N=26)		
Streptococcus pneumonia	13	50.0
Neisseria meningitidis	9	34.6
Haemophilus influenzae	3	11.5
Escherichia coli	1	3.8
CSF with no abnormal finding (of 109)	14	12.8

Identification of etiologic agents – Among those who had CSF analysis, causative bacteria was detected in 26 (23.9%) patients. *Streptococcus pneumoniae* was identified in 13 (50%) of them; the other 9 (34.6%) were *Neisseria meningitidis*. One patient, with advanced HIV infection and strongyloides stercoralis hyperinfestation, had *Escherichia coli* meningitis.

Only 14 (51.9%) of those microbiologically confirmed cases were isolated on culture; 8 cases were identified on all the three microbiologic tests (gram stain microscopy, LAT and culture) (**Table 4.10**).

Eleven of the cases with culture positive CSF did not receive any antibiotics before admission. Eight of the culture isolated organisms were *Streptococcus pneumoniae* cases. With regard to antibiotic susceptibility pattern, *S. pneumoniae* showed very high sensitivity for ceftriaxone and penicillin. All of the eight culture positive cases were susceptible to ceftriaxone whereas 7 were found to be responsive for penicillin. However, sensitivity of this organism against chloramphenicol, co-trimoxazole, ciprofloxacin and gentamycin was found to be low.

Only three of the *Neisseria meningitidis* cases were isolated from culture. All were susceptible to penicillin but one case was found to be resistant against ceftriaxone.

The *Escherichia coli* isolated in HIV patient showed extended betalactamase phenotype, being resistant against penicillin, amoxicillin/clavulanic acid and cephalosporin. It was found to be susceptible to gentamicin only.

In five patients, fungal etiologies were isolated; four *Cryptococcus neoformans* and one *Candida albicans*. All of them were HIV patients.

Other laboratory tests

All patients had complete blood count, HIV test and blood film test for hemoparasite during their current admission. Leucocytosis (White count>11000/µL) was detected in 62 (48.8%) patients; 54 (42.5%) had anemia as defined by WHO (13g/dL for men and <12g/dL for women), but only 10 (7.9%) had severe forms (hemoglobin <8g/dL). The only acute phase reactant possible to do was erythrocyte sedimentation rate (ESR) which was found to be elevated in 78.6% of those who had the test; in 38.1% the elevation was significant (>50) (**Table 4.11**).

Among HIV positive patients, 13 of the 16 who had CD4 count recently had <200 cells/µL (severe immune suppression). On WHO's clinical staging, all of the HIV patients were at stage 3 or 4.

The rate of co-infection with plasmodium species was very low with only two cases of *Plasmodium vivax* cases detected (**Table 4.11**).

Table 4-11 – Other laboratory tests done for patients treated as bacterial meningitis at Jimma University Hospital, Ethiopia

Tests done	**Number**	**Percent**
Complete blood count	127	100
Erythrocyte sedimentation rate (ESR)	84	66.1
HIV test*	127	100
CD4 count (for HIV patients only)	16	69.6
Blood film for hemoparasite†	127	100
Findings		
White cell count		
<4000	10	7.9
4000-11000 (normal)	55	43.3
>11000	62	48.8
Hemoglobin		
Normal	73	57.5
Anaemic (<13 for men, <12 for women)	54	42.5
Platelet (N=127)		
≥150,000/µL (normal)	109	85.8
50000-149,000	13	10.2
<50,000	5	3.9
ESR (N=84)		
Normal (0-20)	18	21.4
21-50	34	40.5
>50	32	38.1
CD4 count (N=26)		
<200	13	81.3
200-349	2	12.5
≥350	1	6.3
Blood film for malaria (N=127)		
Positive	2‡	1.6

*Test was considered as done in patients with already known HIV even though it was not done this time

† Blood film was repeated at least twice in all of them

‡ Both cases were *Plasmodium vivax*

Clinical category of patients based on case definition

Overall, 90 patients had fulfilled clinical and/or laboratory evidences compatible with bacterial meningitis. Fourteen cases even though they were treated empirically with antibiotics for bacterial meningitis had normal CSF findings; 23 had clinical evidence suggestive of other

diagnosis. Of the patients with compatible clinical and laboratory evidence for BM, 14 were additionally treated for other differential diagnosis (**Figure 4.7**).

Apart from their CSF findings, patients with diagnosis other than bacterial meningitis had the following differences when compared to those with BM. Longer duration of symptoms (10.2±5.8 versus 4.7±3.8 days, $p<0.001$); focal neurologic abnormalities (hemiparesis, P=0.019 and cranial nerve palsy, P=0.041) and were less likely to have fever at presentation (69.6% versus 96.2%, p=0.01).

Twenty of patients treated for other diagnosis received treatment for tuberculous meningitis; however, its diagnosis was not confirmed. Five patients with confirmed fungal meningitis (see above) were treated with antifungal agents. Among 23 patients who fulfilled case definition for other differential diagnosis, treatment initiation for the differential diagnosis had a delay of 2.5 days on average (SD=1.5).

Ceftriaxone given as 2gm intravenously twice daily was the main stay of treatment; used as the only antibiotics in 91 patients and in combination with other antibiotics in 35 patients. Only in one patient was the combination of crystalline penicillin and chloramphenicol used. Forty-two (33.1%) of the patients were also given adjunctive dexamethasone treatment.

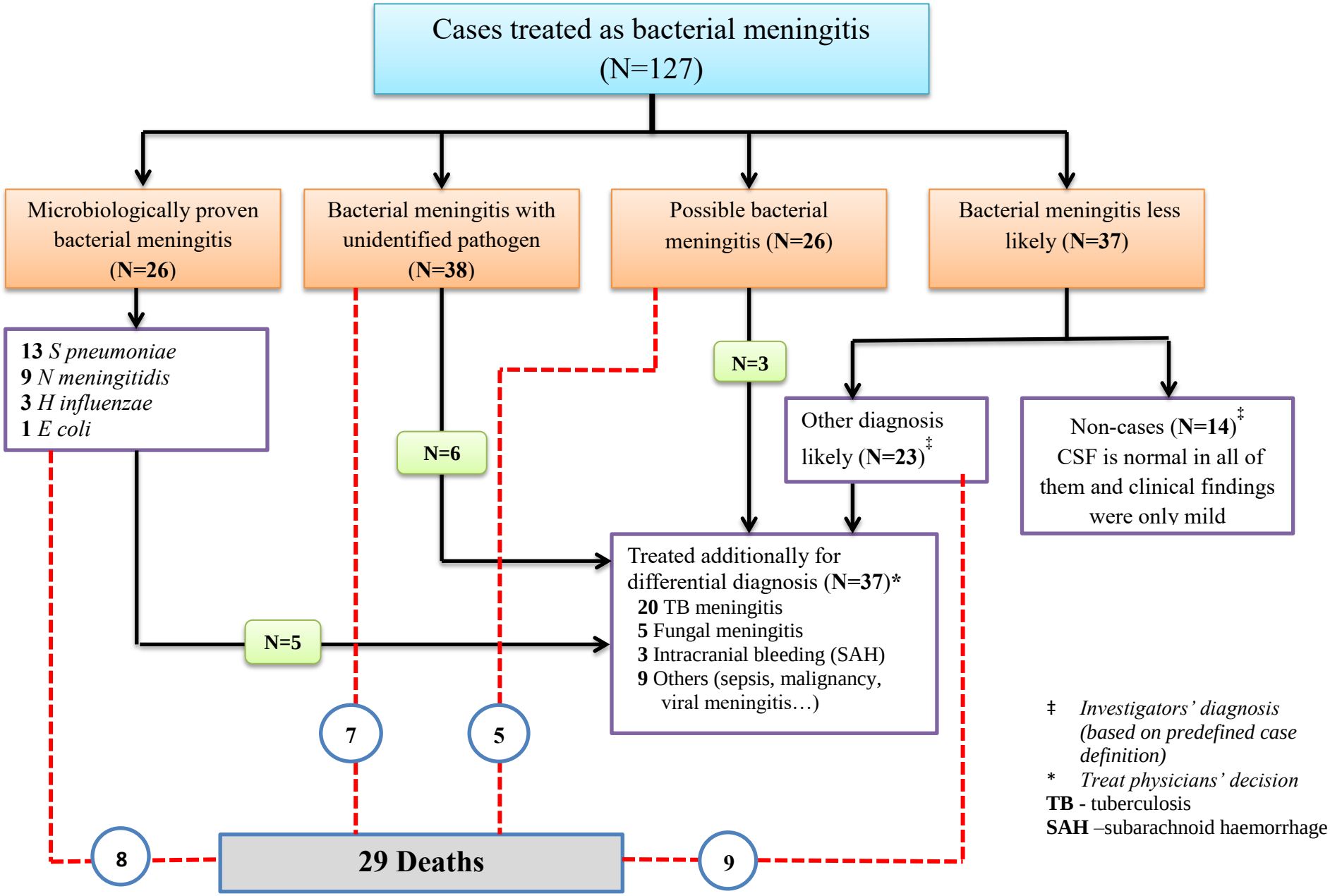


Figure 4-7 – Clinical category of patients treated as bacterial meningitis based on predefined case definitions and their mortality at discharge, Jimma University Specialized Hospital, Ethiopia

Seasonal variability of cases

The number of cases treated each year did not show uniform seasonal variability often described during outbreaks of meningococcal meningitis outbreak. However, the peaks for each year occurred during period of either January to March or October to December. On the other hand, the lowest number of cases recorded each year was during the rainy seasons of June to September. However, except for 2014, there was paradoxical increase in number of cases in August (**Figure 4.8**).

Apart from seasonal variability, there were also differences in number of cases treated as bacterial meningitis each year. The data was collected for 10 months in 2013. Despite this, the highest number of patients was seen that year with 50. This fell to 36 and 41 in subsequent years despite full 12 month months of data collection each.

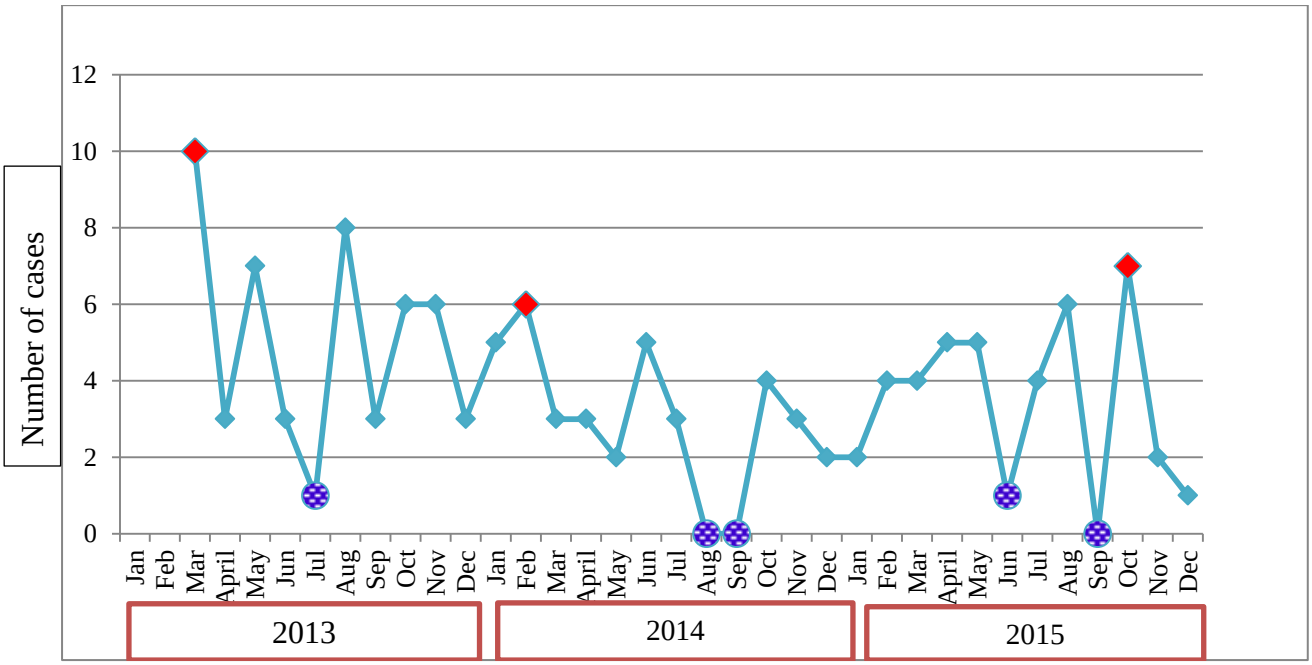


Figure 4-8 – Trends in the number of cases admitted to Jimma university hospital with bacterial meningitis between 1 March, 2013 to 31 December 2015

Hospital course and discharge outcome

Patients were followed daily with vital sign assessment and neurosign charts. Most patients had good response of their fever to antibiotic treatment. However, in 34 (28.1%) patients, the fever persisted beyond the second day of inpatient antibiotic treatment. Among patients who had impaired consciousness on presentation, 29 (45.3%) regained it within the first 3 days of

inpatient treatment. However, 24 (37.5%) of patients in this group did not regain their conscious till their death or discharge from the hospital.

The average length of hospital stay was 13 days (SD=9) with range of 12 hours to 50 days. The mean duration of hospital stay in those who survived to discharge was 14.3 days (SD=8.7). Among deceased patients, the deaths occurred in the first 5 five days of admission in 15 (53.6%) of them.

Multivariate linear regression models identified significant positive correlation between length of hospital stay (LOS) and the following variables: identification of bacterial etiology, HIV infection and presence of evidence for other differential diagnoses. Accordingly, patients who had evidence of other differential/additional diagnosis stayed 5.8 days (1.98-9.66) longer than those who did not (p=0.003). Similarly, HIV infected patients stayed 5 more days (0.25-9.62) than those who were seronegative (P=0.039). On the other hand, patients with microbiologically proven meningitis had 5 additional days (0.74-9.94) in the hospital than the rest of the patients (p=0.024) (**Table 4.12**).

Table 4-12 – Predictors of length of hospital stay in multiple linear regression with stepwise entry, controlled for age and sex

Independent variables	Regression Coefficients (B)	Std. Error	t	P	95% CI for B	
					Lower Bound	Upper Bound
Alternative Diagnosis	5.821	1.927	3.021	0.003	1.983	9.659
Etiology identified	5.339	2.312	2.309	0.024	0.735	9.944
HIV positive	4.934	2.352	2.097	0.039	0.248	9.619

Outcome on leaving hospital – 76 (60%) patients were discharged with improvement, 9 left the hospital in the same condition, while 13 were discharged with some improvement but with apparent neurologic sequelae. Eighteen patients (14.2%) left the hospital against medical advice (self-discharged).The mortality rate in the hospital was 22.8% (29 deaths). Among survivors, 19 (19.4%) had unfavorable GOS (2-4).

Headache and evidence of neurologic sequelae were the commonest symptoms at discharge. Among survivors, 18 (18.4%) had neurologic sequelae. Hemiparesis and coma were the commonest neurologic complication identified (**Table 4.13**).

MMSE was completed for only 72 of the survivors; its administration was limited by poor literacy status of these participants. Six (8.3%) of them had score of <24 at discharge from the hospital.

Table 4-13 – Discharge clinical characteristics of patients treated as bacterial meningitis at Jimma University hospital

Variables	**Total, N=127**	**Proven BM, N=26**	**BM with unknown etiology, N=38**	**Possible BM, N=26**	**BM doubtful, N=37**
Status on leaving hospital	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Full recovery	76 (59.8)	14 (53.8)	23 (60.5)	18 (69.2)	21 (56.8)
Some improvement	13 (10.2)	4 (15.4)	6 (15.8)	3 (11.5)	0
The same condition	9 (7.1)	0	2 (5.3)	0	7 (19.9)
Death	29 (22.8)	8 (30.8)	7 (18.4)	5 (19.2)	9 (24.3)
Glasgow outcome scale					
Favorable (5)	79 (62.2)	13 (50)	26 (68.4)	18 (69.2)	22 (59.5)
Unfavorable (1-4)	48 (37.8)	13 (50)	12 (31.6)	8 (30.8)	15 (40.5)
Discharge symptom† (among survivors, N=98)					
Headache	18 (18.4)	3	4	5	6
Fever	5 (5.1)	1	1	1	2
Body weakness (hemiparesis)	5 (5.1)	1	0	0	4
Abnormal body movement (convulsion)	4 (4.1)	1	0	1	2
Uncommunicative	4 (4.1)	1	1	0	2
Nuchal rigidity	4 (4.1)	1	1	1	1
Hearing difficulty	3 (3.1)	2	1	0	0
Blurring of vision	2 (2.0)	2	0	0	0
Others‡	12 (12.2)	3	5	3	1
Neurological sequelae (N=18)	18 (18.4)	5	2	1	10
Hemiparesis	5 (27.8)	1	0	0	4
Coma	5 (27.8)	1	1	0	3
Seizure	4 (22.2)	1	0	1	2
Decreased hearing (self-reported)	3 (16.7)	2	1	0	0
Facial palsy	2 (11.1)	0	0	0	2
MMSE (total evaluated = 72)					
≥24	66 (91.7)	11	20	16	19
<24	6 (8.3)	1	2	0	3

† Seven patients had two or more symptoms listed
‡includes easy fatigability, poor appetite, feeling of unwellness
MMSE – Mini-mental state examination

Table 4-14 – Univariate analysis of factors associated with unfavourable discharge outcome

Variable	Favorable outcome	Unfavorable outcome	OR (95%CI)	P
Age (Y), mean(SD)	32.2 (13)	33.6 (13.6)		0.564
Gender				
Women	30 (62.5%)	18 (37.5%)	*Reference*	0.957
Men	49 (62.0%)	30 (38.0%)	1.02(0.49;0.2.14)	
HIV infection				
No	68 (65.4%)	36 (34.6%)	*Reference*	0.121
Yes	11 (47.8%)	12 (52.2%)	2.06(0.83;5.132)	
Pneumonia				
No	7 (30.4%)	16 (69.6%)	*Reference*	0.001*
Yes	72 (69.2%)	32 (30.8%)	5.14(1.93;13.712)	
Time to antibiotics, h	101.6	168.3		<0.001*
≤48hours	31 (77.5%)	9 (22.5%)	*Reference*	0.014*
>48 hours	48 (55.2%)	39 (44.8%)	2.80 (1.19;6.57)	
Adjunctive dexamethasone				
No	63 (74.1%)	22 (25.9%)	*Reference*	<0.001*
Yes	16 (38.1%)	26 (61.9%)	4.65 (2.11;10.25)	
GCS, score of 15	14	12		<0.001*
>8	76 (66.1%)	36 (33.9%)	*Reference*	0.006*
≤8	3 (25%)	9 (75%)	5.85 (1.5;22.83)	
Hypotension	3 (37.5%)	5 (62.5%)	2.95 (0.67;12.93)	0.144
Seizure	15 (53.6%)	13 (46.4%)	1.63 (0.70;3.82)	0.262
Neurologic deficit	2 (22.2%)	7 (77.8%)	6.57 (1.31;33.1)	0.011*
CSF appearance				
Clear	43 (78.2%)	12 (21.8%)	*Reference*	0.032*
Turbid	32 (59.3%)	22 (40.7%)	2.46 (1.06;5.70)	
CSF glucose ratio (mean)	0.50	0.37		0.025*
CSF protein, mg/dl (mean)	106.6	130.7		0.259
CSF WBC, cells/µL (mean)	2113	3577		0.419
Causative bacteria				
Others	8 (61.54%)	5 (38.46%)	*Reference*	0.237
Streptococcus pneumoniae	5 (38.46%)	8 (61.54%)	2.56 (0.53;12.43)	
Evidence supporting other diagnosis				
No	67 (74.4%)	23 (25.6%)	*Reference*	<0.001*
Yes	12 (32.4%)	25 (67.6%)	6.07 (2.632;14.0)	
Fever persisting after 2 days				
No	71 (81.6%)	16 (18.4%)	*Reference*	<0.001*
Yes	8 (23.5%)	26 (76.5%)	14.42 (5.52;37.68)	

**Statistically significant*

Factors associated with unfavorable outcomes

In univariate logistic regression analysis, the following variables were found to be associated with unfavourable outcome: time to antibiotic treatment, presence of concomitant pneumonia, treatment with dexamethasone, low GCS on admission, neurologic deficit (hemiparesis or

cranial nerve deficit) on presentation, turbid CSF findings, low CSF glucose ratio, clinical clues supporting other diagnosis (TB meningitis, cryptococcal meningitis) and persistent fever after 2 days (**Table 4.14**).

On multivariate analysis, the effect of most of these variables disappeared except for adjunctive dexamethasone treatment, persistent fever and HIV infection, the effect of which came into picture in multivariable analysis. However, the effect of these three variables is weak due to wide confidence interval (**Table 4.15**).

Table 4-15 – Multivariate analysis of factors associated with unfavourable outcome (stepwise conditional logistic regression method).

Variable	AOR	95.0% CI	P
Dexamethasone treatment	6.79	1.46-31.48	0.014
Fever after 48hrs	25.0	5.55-112.59	<0.001
HIV infection	17.87	3.23-98.78	0.001

Key findings from prospective study (summary)

Of the 127 participants, 85% were < 50 years of age. Fever, headache and nuchal rigidity were the major presenting symptoms. Half them also presented with impaired consciousness. Duration of illness before presentation was 5.6days (SD=4.7). The rate of HIV infection was 18.1%. Twenty-three (18.1%) were diagnosed with comorbid pneumonia.

CSF was analysed in 109 (85.8%) of patients however, only 90 (70.9%) of patients had evidences compatible with bacterial meningitis; only 26 of them had etiologic bacteria identified. *S. Pneumoniae* and *N. meningitidis* were the major causes.

The in hospital mortality rate was 22.8% whereas, 18.4% of survivors had neurologic sequelae on discharge. HIV infection, fever persisting after 2 days of inpatient management and dexamethasone therapy were independently associated with increased mortality.

5. Discussion

The findings in the two studies revealed that the care of patients with bacterial meningitis in tertiary hospitals in Ethiopia is hampered by multiple factors. In retrospective study, only 236 (55.5%) patients had CSF analysis and a causative bacterium was identified in only 14 of them. Most, 109 (85.8%) patients in the prospective study had CSF analysis. However, etiologic agent for BM was identified in 26 (20.5%) patients only. In both studies, cases treated as BM in teaching hospitals in Ethiopia were found to have high mortality. Some of the major challenges identified were: (i) Patient with suspected bacterial meningitis did not receive proper diagnostic tests. (ii) The time from onset of illness to hospital presentation was found to be longer than most studies from high income settings. (iii) More than quarter of the patients have taken antibiotics in the community before hospital presentation. (iv) The rate of HIV infection was found to be very high as compared to community prevalence. Presence of HIV infection in patient with meningitis is associated with poor discharge outcome. (v) Dexamethasone treatment was associated with an increased mortality.

Though there were significant differences in data quality based on the study designs, the findings from the prospective and retrospective studies were highly concordant. The classic triad of bacterial meningitis (fever, headache and neck stiffness) were present in more than 80% of patients. The time from symptom onset to hospital presentation of 5 days on average is higher than most findings from other settings (2, 3, 38). In addition to this, there was high rate of antibiotic use in the community for similar complaint before presentation (24.5% in retrospective and 34.6% in prospective), a finding consistent with previous report from the country (48). The former is the likely cause for the delay of presentation. This might have resulted in patients presenting with poor clinical status: about half of the patients presented with impaired consciousness. Over 10% of patients presented with evidence of pulmonary aspiration with clinically evident pneumonitis. This probably reflects a prolonged period of loss of consciousness before presentation.

The diagnosis of BM in the study settings was based mainly on clinical ground with no proof of the etiologies. The prospective design oversaw strict collection of CSF specimen (unless contraindicated or technically difficult) and its analysis, however, 44.5% of patients in the retrospective wing did not have CSF analysis. Moreover, 37 (29.1%) in prospective and 133

(31.3%) patients in retrospective group were given antibiotics despite the lack of evidence supporting the diagnosis of bacterial meningitis at all. Hence, patients included in the studies could have additional or alternative diagnoses other than BM. As a result, the reported morbidities, mortalities and disabilities may not directly relate to bacterial meningitis.

The findings suggest that there is very low threshold to diagnose and treat bacterial meningitis in the setting despite lack of clear evidence for it. This may be due to the fact that BM is associated with high mortality and is fatal in most untreated cases (53). On the other hand, evidence-based guidelines are lacking for management of BM in resource poor settings (3, 16). These reasons might have led physicians to take pragmatic approach of empiric management of suspected cases without laboratory confirmation. However, such an approach may contribute to a poor outcome because the antibiotic sensitivity pattern is unknown and it can lead to the under-diagnosis or delay in treatment of other central nervous system (CNS) infections (16).

Overall, the findings from this project can be seen from two major perspectives: (1) Strategies used for case management and (2) Treatment outcome of patients. Seasonality of the disease will also be discussed briefly.

5.1. Case management strategies

Assessment of management strategies for BM was the major focus of the retrospective study. It identified critical gaps at three levels in the management of bacterial meningitis in teaching hospitals in Ethiopia. (i) 44.5% of patients did not have lumbar puncture (ii) 42% of those who had their CSF specimen collected did not get proper analysis, and (iii) 140 patients who had CSF analysis (among suspected unproven cases and non-cases) were treated as BM despite findings that did not support the diagnosis.

However, about half of the patients presented with impaired consciousness and close to 10% had focal neurologic deficits both of which may be indicators of an increased intracranial pressure (54). Such patients should ideally have CT scanning before LP (11, 55), which is not widely available in the country and non-existent at all the hospitals during the study period. This may be a reason for the cautious approach by physicians in terms of undertaking LP. Additionally, lack of LP kits, shortage of supply for common CSF tests and skill gaps by

professionals (56) could also be the reason. Furthermore, many patients with non-suggestive (normal) CSF findings were still treated as BM. This may be due to treating physicians' lack of confidence on laboratory results, an issue which needs further investigation.

Empiric antibiotic choices for bacterial meningitis vary based on age, the setting and local antibiotic sensitivity pattern (11, 17). Combination of ceftriaxone and vancomycin is recommended in high income countries and in settings where penicillin resistance is common (12). However, data for antibiotic sensitivity in sub-Saharan Africa is scarce. Thus, antibiotic option is based on local availability and cost of the drugs (3, 57). WHO recommends ceftriaxone alone as treatment of choice in non-epidemic meningitis in Africa (57).

On the other hand, standard treatment guideline by Drug Administration and Control Authority of Ethiopia (recently renamed as Ethiopian Food, Medicine and Health Care Administration and Control Authority) recommends ceftriaxone and vancomycin as first choice, adopting the recommendation from high income countries. It also recommends penicillin and chloramphenicol as second options (58). However, there is no large scale published national data on local antibiotic sensitivity pattern and cost-effectiveness to support this recommendation. Recent small scale studies in the country revealed that *S. pneumonia* is highly sensitive to ceftriaxone (59) and penicillin (47, 59, 60). Similar susceptibility pattern for *S. pneumonia* was found in the current study.

For individuals older than 50 years and those with immune suppression, empiric treatment should include antibiotics against Listeria monocytogenes (8, 11). Similarly, the Ethiopian standard treatment guideline for general hospitals (58) and guidelines in developed countries (12) recommend ampicillin in such patients. Even though there is a tendency to use it more in older patients in this study, it was not universally administered in patients with the indication. For instance, only 26.1% of patients older than 50 years and 4.3% of HIV patients were given ampicillin.

Adjuvant corticosteroid in management of bacterial meningitis in high income countries is now part of standards of care in BM (61, 62). However, its benefit in low and middle income countries has become highly contentious and its routine use in such settings has never been supported with strong evidence (38, 63, 64). Despite this, national standard treatment guidelines of some countries in sub-Saharan Africa have kept recommending its routine use

(58, 65), an adoption of recommendation for high income countries (61, 62). The finding in our study, where dexamethasone was used in half of the patients, is a testimony of scepticism towards the current recommendation in low income countries. However, its uncontrolled use in settings with high HIV prevalence and those with potential alternative diagnosis may be deleterious.

In general, the finding from all the hospitals in this study does not strictly conform to one recommendation. This shows lack of local evidence-based case management strategies and absence of consensus among clinicians and hospitals. It also reflects a decline in use of penicillin and chloramphenicol in the management of BM in the country.

In addition to empiric treatment for BM, physicians at each hospital have also tried to address common differential diagnosis including cerebral malaria, tuberculous meningitis and viral meningitis. Even though the effort and responsiveness of treating physicians to the situation at stake should be commended, care should be made to avoid unnecessary use of antimicrobial agents. Such empiric therapy may also delay management of other potential disorders of the central nervous system.

The challenges in diagnosis and treatment of serious infectious diseases in the country may not be limited to bacterial meningitis and teaching hospitals. Even though this study was limited to such hospitals, the situation in primary hospitals in the country may not be different or even worse. This may result in a serious consequence on overall health care system in the country. First of all, over/unnecessary antibiotic prescription may contribute to the ever increasing antimicrobial resistance. Secondly, it may result in overutilization of the limited resource in terms of unnecessary admission and intravenous antibiotic use.

5.2. Treatment outcome

The overall outcome assessment on leaving hospital revealed that 156 (36.7%) in the retrospective study and 48 (37.8%) in the prospective study had unfavorable outcome (GOS 1-4). The in hospital mortality rates of 22.8 % in prospective and 20.2% in retrospective are comparable with findings from high income countries; 21% in the Netherlands (2), 21% in Sweden (66) and 26% in USA (33). When compared to findings from low income countries, Malawi for instance with in hospital mortality of over 40% (7, 20), the findings in these studies is much lower than expected in the setting. However, the findings in the current

studies may not reflect the real mortality associated with BM in the country. This is because the diagnosis of BM in several of the patients was unclear and it is likely that many of these patients suffered from diagnosis other than BM.

Furthermore, it should also be noted that a relatively low prevalence of HIV in our study (5.4% and 18.1%) makes a comparison with Malawi study difficult because of high prevalence (>90%) in that study.

The documented short-term neurologic sequela in survivors was 18.4% (prospective) and 11.2% (retrospective), lower than in most reports on the outcome of BM (2, 7, 20, 33, 35, 66). As there is no trend of routine neurologic evaluation at and after discharge of patients with meningitis, only severe and symptomatic forms were included here. These findings did not include subtle sensory neural hearing loss which was difficult to assess.

In addition to this, due to the fact that significant proportion of patients in these studies had potential alternative diagnosis, the reported finding may not reflect the true problem. The difference in findings between the prospective and the retrospective is a proof for this and may be due to the difference in quality of data and characteristics of the participants. In complement with this, subgroup analysis in retrospective study based on case definition revealed higher rate of neurologic sequelae (15.6%) in those with CSF evidence for bacterial meningitis (possible and confirmed cases) versus 7.0% in the others. These all reflect that the overall neurologic sequelae in patients with bacterial meningitis in the setting would be much higher than reported here had there been standard evaluations for their presence.

Because of the design problem and poor documentation in the setting, a common problem for the retrospective study, the morbidities reported could also be an underestimate in true BM. Moreover, significant proportions of the patients left the hospital against medical advice or were referred to other centres for better care. Most patients in these groups had a poor clinical status at leaving the hospital as compared to the other groups (**Table 4.13**). This could have also resulted in underreporting of the true mortality and complications related to the cases.

With exception to adjunctive dexamethasone treatment (see below), the factors associated with poor outcome are in line with most of the studies from low income and high income countries (2, 7, 9, 20, 33, 64, 66). Impaired levels of consciousness along with longer duration of symptoms before hospital presentation were main reasons for occurrence of

aspiration pneumonia. Their presence altogether contributed highly for unfavorable outcome (2, 27).

The effect of HIV infection on outcome came to picture in prospective study only which showed an independent association with unfavorable outcome albeit wide confidence interval. This effect could have been underpowered due to small sample size. Nevertheless, the effect of advanced HIV infection on outcome of serious bacterial infections like BM is not an overstatement even though evidence from well-designed studies is limited (36). Moreover, the rate of HIV infection of nearly 20 times that of the community prevalence [18.1% versus 1.14% (67)] reflects a significant interaction. Large scale prospective studies from settings with high prevalence of both conditions are needed to uncover their overlaps, effect on outcome and best treatments in such conditions.

However, conventional poor prognostic indicators like etiologic bacteria and age of patients were not found to be associated with adverse outcome. The study was not able to detect an effect of these factors due to small number of confirmed cases and due to the fact that only outcome at leaving hospital was assessed. Furthermore, about 85% of patients were younger than 50 years; fewer cases in the other group might have underpowered the effect of age on outcome.

As described above, the etiologic diagnosis for bacterial meningitis and other differential diagnosis were not possible for majority of patients. This has resulted in mis-diagnosis of other etiologies and hence a delay of their treatment. Patients who fell in this category of diagnosis were found to have unfavorable outcome at discharge. This effect can be due to one or more of the following reasons. First of all, these patients had longer duration of the illness before admission and the treatment for possible diagnosis was started after two days of admission. They also had higher rate of focal neurologic deficit at presentation and treatment with antibiotics in the community. It is more likely that these patients had alternative diagnoses other than bacterial meningitis and tuberculosis, due to the epidemiology, tops the list. It is thus possible that delay of treatment for the tuberculosis or other alternative diagnoses might have contributed to poorer outcome at discharge.

Adjuvant corticosteroid in management of bacterial meningitis in low and middle income countries, and in settings with high HIV prevalence in particular, has never been proven

beneficial (38, 63, 64). To date, there is no recommendation of its use in such settings. However, physicians in settings with little evidence and diagnostic facilities like Ethiopia have continued its use based on recommendation for high income countries (11). The finding in our study, where dexamethasone was used in half of the patients, is a testimony of scepticism towards the current recommendation in low income countries.

This study revealed that there is no any positive outcome associated with dexamethasone treatment in BM. It was rather associated with higher mortality and lower discharge GOS which persisted despite thorough subgroup analysis. Even though lack of evidence for its benefit is consistent with previous findings from similar settings (38, 63, 64) no simple explanation can be given for the negative effects. As it has repeatedly been highlighted in this paper, majority of the cases included in this study did not have confirmed diagnosis of bacterial meningitis. Hence, it is possible that some of the patients could have other alternative diagnoses. Dexamethasone administration in such conditions and other potential brain insults without treating underlying disease condition could have resulted in poorer outcomes. As this is the first study that looked at the effect of dexamethasone in patients treated with presumptive diagnosis of BM, it makes it valuable for the real situation in developing countries.

5.3. Seasonal variability

Bacterial meningitis, meningococcal meningitis in particular, is known for its notorious seasonal variability related to the amount of rain fall (25, 60, 68). Nevertheless, seasonal variability has also been documented in pneumococcal meningitis (20, 69). This seasonal variability in tropical settings is said to be due to more of environmental factor than the etiologic agent (60, 70, 71). Understanding seasonality of meningitis in the area is important for public health intervention (25, 68).

Though there was no uniform pattern in seasonal variability of number of cases in the current studies, the peak number of cases in the dry months and the nadir in the rainy season reflect some patterns consistent with the findings described above (25, 70). Thus, the epidemiologic and environment explanations of these variations cannot be denied. However, the seasonality in these two studies can have more explanation in the study settings. Besides real seasonal variability of the disease, socio-economic factors and infrastructure problems may explain the

differences. Over 60% of the patients were rural residents and farmers. As river volumes increase during rainy months of June to September, roads may be difficult to access hospitals during this time. Moreover, due to subsistent livelihood of these farmers, visiting hospital far from harvest season may be financially difficult.

In addition to these factors, the lost documentation/charts during 2011 and 2012 in retrospective study might have also resulted in lower number of cases during these times. In the prospective study, design effect of the research has likely affected the number of cases since establishment of microbiology late 2013. Number of cases treated as bacterial meningitis since then was less than before but more cases had suggestive CSF findings as compared to previous years.

6. Conclusion and recommendation

These studies indicate that time from onset of illness to hospital presentation is longer than findings in most literatures. Moreover, a significant proportion of patients have been treated with antibiotics for the same problem before hospital presentation. As a result, most patients presented with poor clinical status as evidenced by low GCS and aspiration pneumonitis.

Most patients who were treated for suspected BM did not receive a proper diagnostic workup and were treated only based on clinical suspicion. Besides, the antibiotic choice was not tailored to specific situation and clinical condition of the patient. Moreover, diagnostic and therapeutic practices were found to markedly vary between the hospitals and clinicians.

The rate of HIV infection was found to be much higher than the expected community level prevalence. Most patients with the infection had very low CD4 counts and advanced stage disease on clinical assessment. Its presence was also associated with unfavorable discharge outcome.

Dexamethasone, despite lack of its benefit in such settings, was commonly used as adjunctive treatment. Its use in management of suspected cases of bacterial meningitis was associated with an increased mortality and poor discharge GOS. This finding re-affirms the lack of its benefit and shows that there are potential deleterious effects in low income countries and in unconfirmed cases.

Thus, it is highly recommended that standard treatment guidelines should be extracted from local data and case management should be based on available and cost-effective diagnostic and therapeutic strategies. Large scale nationwide prospective study is mandatory to achieve this goal. To date, there is no evidence supporting the benefit of dexamethasone in suspected or confirmed cases of bacterial meningitis in low income settings. Therefore, physicians should abide by the current recommendation and refrain from its overzealous use in such settings.

7. Limitations

Prospective study – This is a study from single teaching hospital with relatively better setting and trained professions for the country. As a result, the reported outcome may not be representative for nation. Secondly, the outcomes reported included only discharge conditions and overt neurologic sequelae. Thus, the real mortality related to the problem may be more than stated here. Moreover, the small number of confirmed cases might have underpowered the effect of common outcome predictors.

The interruptions and absence of some of the supplies from national marker have resulted in occasional interruption of microbiology services. The fact that there was no CT scan service at the hospital and that full laboratory services were limited to working hours only were other setbacks.

Retrospective study – Poor documentation and lost medical records were limitation during the study. Patients included in the study were not confirmed cases of bacterial meningitis and hence its true outcome could not be addressed in this study. Furthermore, because only teaching hospitals were included in the study, the findings may lack national representativeness and may not reflect the real practice throughout the country. On the other hand, as it is common situation to have interruption of certain diagnostic laboratories and drug supplies in the settings, the diagnostics and therapeutic agents used may be affected by these factors and may not reflect management approach employed by the hospitals and/or practitioners at all times. Nevertheless, it must be assumed that the rate of treatment of cases with suspected BM lacking any diagnostic workup is even higher throughout the country.

8. Challenges

Apart from very few studies presented in the introductory part of this thesis, information regarding morbidity, mortality and case management of BM in the country was few and far between. When the proposal for this project was written, no formal data could be traced regarding bacterial meningitis, and even more broadly, for CNS infections in general at Jimma University Hospital. There was no microbiology unit, no treatment guideline and even no registration for number of cases treated annually with bacterial meningitis. Thus, everything had to start from the scratch. The annual number of cases could only be reviewed from admission registration book which revealed about 90 to 120 admissions due to 'bacterial meningitis'

The initial design of this project was solely prospective with the aim of assessing the impact of HIV infection on outcome of bacterial meningitis in Ethiopia. The project started with the expectation of 100 cases of bacterial meningitis annually as it was found on admission registration book revision during proposal development. The target sample size for this design was 186 confirmed cases of bacterial meningitis (138 HIV negative and 46 HIV positive). However, assessing the data collected in the initial 12 months of data collection revealed that most patients treated as bacterial meningitis were not actually confirmed cases. It was also found that most patients treated as BM at the hospital were not having the disease. As a result, the planned sample was predictably unachievable with this design during the PhD period. Although this finding was not what was initially intended, it revealed a major gap in the management of BM at the hospital.

To supplement this finding, a separate retrospective wing was added to the project with the aim of assessing these gaps of patient care in four teaching hospitals in Ethiopia.

Subsequent plan

1. Make short communication with responsible organizations under federal ministry of health Ethiopia (Food, Medicine and Health care Admiration and Control Authority [FMHACA], Ethiopian Public Health Institute [EPHI])
2. Prepare local guideline with expertise in the field
3. Molecular analysis of over 500 CSF in the storage to investigate bacterial, viral or fungal causes of meningitis

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Annex – 1 Case reporting format for Retrospective study

Assessment of treatment strategies for bacterial meningitis in Ethiopia

I. Identification

1. Initials _____
2. MRN_____
3. Hospital_____
4. Age_____
5. Gender_____
6. Date admitted_____
7. Area of residence
   a. Urban ☐ b. Rural ☐

II. Clinical history at presentation

8. Duration of illness (days)_____ or hours_____
9. Symptoms (check all that apply)
   a. Fever☐
   b. Headache☐
   c. Neck rigidity☐
   d. Vomiting ☐
   e. Photophobia ☐
   f. Loss of consciousness ☐
   g. Seizure ☐
   h. Body weakness☐
   i. Skin rash ☐
10. Any documented risk factor or underlying disease (check all that apply)
    c. Smoker☐
    d. Alcoholic ☐
    e. Diabetes mellitus☐
    f. Pregnancy☐
    g. Known HIV patient☐
    h. Similar illness at home or in the vicinity☐
    i. Other, specify _____
11. Antibiotic treatment for the same complaint before presentation:
    a. Yes☐ b. No ☐
12. If yes, mention the **type** and **route** of administration

    _____

    _____
13. If yes, **when** and for **how long** was the treatment given? (days)_____
14. If yes, **where** was the treatment given
    a. Health centre ☐
    b. Private clinic ☐
    c. Other hospital ☐
    d. At this hospital ☐
    e. Other, specify_____
    f. Not specified ☐

III. Physical examination findings at presentation

15. Vital signs
    a. T (^{0}C)_____
    b. PR (bpm)_____
    c. RR (per minute) _____
    d. BP (mmHg)_____
16. GCS_____

Data accuracy and completeness is essential for evidence based practice! 1

17. Cranial nerve palsy (III, VI, VII)
    a. Yes, specify_____
    b. None ☐
18. Hemiparesis/hemiplegia
    a. Yes☐ b. No☐

IV. Laboratory findings

19. Was LP done
    a. Yes ☐ b. No ☐
20. If **no**, mention the reason_____

If yes to Q19, ANSWER Q21 THROUGH 30. If NO, go directly to Q31

21. CSF Appearance
    a. Crystal clear☐ c. Bloody ☐
    b. Turbid☐
22. **A**. CSF Glucose (mg/dl)_____ **B**. CSF glucose to serum glucose ratio_____
23. CSF Protein (mg/dl)_____
24. CSF cell count (per HPF)_____PMN(%)_____Lymphocyte (%)_____
25. Gram stain finding
    a. Positive☐ b. Negative☐ c. Not done☐
26. If positive, give all the descriptions here _____

    _____

    _____
27. Indian ink
    a. Positive☐ b. Negative☐ c. Not done☐
28. ZN stain for AFB
    a. Positive☐ b. Negative☐ c. Not done☐
29. CSF culture and sensitivity test?
    a. Positive ☐ b. Negative☐ c. Not done ☐
30. If positive, give the type of organism and their sensitivity pattern

    _____

    _____

Complete Blood count (CBC) – Q31-33

31. WBC (per µl)_____
    Neutrophils (%) __ Lymphocytes (%) __ Others cells (%) __

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32. Hb(g/dl)_____

33. Platelet (per µl)_____

34. ESR _____mm/in the first hour

35. Blood glucose (mg/dl)_____

36. HIV rapid test

a. Positive☐ b. Negative ☐ c. Not done☐

Answer Q37 to 40 if HIV positive, if not, go directly to Q41

37. What is the current WHO stage? _____

38. What is the CD4 count? _____

39. Is the patient on HAART?

1. Yes ☐ 2. No ☐

40. If on HAART, for how long? (years) _____OR months_____

41. Blood film for haemoparasite

a. Positive☐ b. Negative☐ c. Not done☐

Mention the finding if positive_____

V. Treatment

42. Mention the **regimen**, **route**, **dose** and **duration** of antibiotic treatment

_____

_____

_____

43. Was dexamethasone given

a. Yes☐ b. No ☐

44. If there is additional treatment given for additional or underlying disease

_____

_____

_____

VI. Outcome assessment

45. What was the outcome at leaving service?

a. Improved☐ b. Died☐ c. Left against medical advice☐

46. Total stay in hospital in **days** _____or **hours**_____

47. GOS at leaving hospital_____(*please complete the details on separate questionnaire for GOS*)

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48. Symptoms at discharge if any_____

_____

49. Discharge neurologic sequalae if any_____

_____

50. If there are other meningitis related complications document at discharge, give it here_____

_____

51. Complete discharge assessment

    a. Complete improvement☐
    b. Some improvement☐
    c. No improvement☐

52. Is discharge diagnosis different from admission?

    a. Yes☐ b. No☐

53. If yes to Q52, give full diagnosis at discharge_____

_____

54. In case of in hospital death, what was the possible immediate cause of **death**?

    a. Brain herniation☐
    b. Respiratory failure☐
    c. Septic shock ☐
    d. Multisystem organ failure☐
    e. Other, specify_____

    _____

Completed by_____ Sign._____ Date_____
Checked by _____ Sign. _____Date _____

Annex – 2 Case reporting format for Prospective study

IMPROVING QUALITY OF CARE IN PATIENTS WITH ACUTE BATERIAL MENINGITIS AT JUSH	Admission assessment

JU – LMU LINK

Initials _____ MRN_____

Age_____ Gender_____ Date admitted_____

I. Demographic characteristics

1. Age (years)_____
2. Gender:
   a. Male ☐ b. Female ☐
3. Area of residence
   a. Urban ☐ b. Rural ☐
4. Distance from hospital in km_____

II. Assessment of risk factors for meningitis

5. Which of the following history apply to the patient (check all that apply)
   a. Smoker☐
   b. Alcoholic ☐
   c. Diabetes mellitus☐
   d. Pregnancy☐
   e. Known HIV patient☐
   f. Similar illness at home or in the vicinity☐
   g. Other, specify _____
6. Have you ever taken vaccine against N.meningitidis (during meningitis epidemics)?
   a. Yes ☐ If yes when? _____
   b. No ☐
   c. Unknown ☐

III. Clinical manifestations at presentation

7. Duration of illness (hours)_____
8. Symptoms (check all that apply)
   a. Fever☐
   b. Headache☐
   c. Neck rigidity☐
   d. Vomiting ☐
   e. Photophobia ☐
   f. Loss of consciousness ☐
   g. Seizure ☐
   h. Body weakness☐
   i. Skin rash ☐
9. Antibiotic treatment for the same complaint before presentation:
   a. Yes☐ b. No ☐
   If yes, mention when, the type, and route of administration
   _____
   _____

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10. Vital signs
    a. T (^{0}C)_____
    b. PR (bpm)_____
    c. RR (per minute) _____
    d. BP (mmHg)_____
    e. BMI (Kg/m^3)_____
    f. [Use MUAC if BMI is not convenient (mm)_____]

11. Chest examination finding
    a. Normal
    b. Abnormal, specify_____

12. Petechial rash on skin
    a. Yes☐ (If any, *include picture*) b. No☐

13. Central nervous system examination
    12.1. GCS_____
    12.2. Mini-mental examination score (if conscious), use MMSE chart to assess____
    12.2 Funduscopy
    a. Normal☐ b. Abnormal☐
    Specify if abnormal_____
    12.3 Cranial nerve palsy (III, VI, VII)
    a. None ☐
    b. Yes, specify_____
    12.4 Hemiparesis
    a. Yes☐ b. No☐

IV. Treatment

14. How long after onset of symptoms was the antibiotics started? (hrs)_____

15. Mention the regimen, route and dose _____
    _____
    _____

16. Was dexamethasone given
    a. Yes☐ b. No ☐

Date of Assessment _____

Completed by_____ signature_____

Checked by_____signature_____date_____

Data accuracy and completeness is essential for evidence based practice!

IMPROVING QUALITY OF CARE IN PATIENTS WITH ACUTE BATERIAL MENINGITIS AT JUSH	Laboratory evaluation

JU – LMU LINK

Initials _____ MRN_____

Age_____ Gender_____ Date admitted_____

I. Lumbar puncture

1. Was LP done
   a. Yes ☐ b. No ☐
2. If no, mention the reason_____
3. If yes, how long after presentation?
   a. Just at presentation(before starting antibiotics) ☐
   b. After antibiotics but within 24hrs of presentation ☐
   c. After 24hrs of presentation ☐

II. CSF profile

4. Opening pressure (cmH_2O)_____
5. Appearance
   a. Crystal clear☐ c. Bloody ☐
   b. Turbid☐
6. Biochemical test
   a. Glucose (mg/dl)_____ Blood glucose (mg/dl)_____
   b. Protein (mg/dl)_____
7. Microscopy
   a. Cells (per HPF) _____PMN (%) _____Lymphocytes (%) ____
   b. Gram stain finding
      i. Gram positive diplococcic (S. pneumonia) ☐
      ii. Gram negative diplococcic (N. meningitides) ☐
      iii. Others, describe_____
   c. Indian ink (for HIV positive patients only)
      i. Positive☐ ii. Negative ☐
   d. ZN stain for AFB (only in case of HIV or culture negative)
      i. Positive☐ ii. Negative ☐

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8. Culture and sensitivity test from CSF

Bacteria identified		Penicillin	Ceftriaxone	Ampicillin	Gentamycin	Chloramphenicol	Ciprofloxacin
1.							
2.							
3.							
4.							

III. Other laboratories

9. CBC
   a. WBC (per µl)_____
      i. Neutrophils (%) ____
      ii. Lymphocytes (%) ____
      iii. Others cells (%) _____
   b. Hb(g/dl)_____
   c. Platelet (per µl)_____
10. CRP_____ or ESR_____
11. HIV rapid test
    a. Positive☐ b. Negative ☐
12. If HIV positive:
    a. What is the current WHO stage? _____
    b. What is the CD4 count? _____
    c. Is the patient on HAART?
       i. Yes ☐ ii. No ☐
    d. If on HAART, for how long? (months) _____
13. B/F: mention the finding_____

Date of Assessment _____

Completed by_____ signature_____

Checked by_____signature_____date_____

IMPROVING QUALITY OF CARE IN PATIENTS WITH ACUTE ATERIAL MENINGITIS AT JUSH | **Vital sign follow-up sheet**

JU – LMU LINK

Initials _____ MRN_____

Age_____ Gender_____ Date admitted_____

Time from admission (hrs) & date	Local time	PR (bpm)	RR/min	$T^{0}(^{0}C)$	BP (mmHg)	Pain score (___/10)	Remark (Improving, The same, deteriorating)
0 (.....)							
4							
8							
12							
16							
20							
24							
28							
32							
36							
40							
44							
48							
52							
56							
60							
64							
68							
72							
76							
80							
84							
88							
92							
96							
100							

Overall Remark: - Improved ☐ Died ☐ The same condition ☐

Date finalized _____

Completed by_____ signature_____

Checked by_____signature_____date_____

Please keep the data as accurate and complete as possible!

IMPROVING QUALITY OF CARE IN PATIENTS WITH ACUTE BATERIAL MENINGITIS AT JUSH | **Daily clinical assessment (Neuro-sign chart)**

JU – LMU LINK

Initials _____ MRN_____

Age_____ Gender_____ Date admitted_____

[*Use (✓) for those that apply*]

Day (from admission)	Headache	Vomiting	Seizure	Hearing problem	GCS (.../15)	Meningeal signs	Cranial nerve palsy	Hemiparesis
0								
1.								
2.								
3.								
4.								
5.								
6.								
7.								
8.								
9.								
10.								
11.								
12.								
13.								
14.								
15.								
16.								
17.								
18.								
19.								
20.								

If there is any additional remark_____

Overall Remark: - Improved ☐ Died ☐ The same condition ☐

Date finalized _____

Completed by_____ signature_____

Checked by_____signature_____date_____

accuracy and completeness is essential for evidence based practice!

Jimma University, Bacterial Meningitis outcome Assessment Questionnaire	Discharge condition assessment form

Initials _____ MRN_____

Age_____ Gender_____ Date admitted_____

Date of discharge_____

1. Total stay in the hospital_____ (days)
2. Which of the following symptoms do you have? (Check all that apply)
   a. Headache☐
   b. Fever ☐
   c. Neck pain☐
   d. Seizure☐
   e. Body weakness☐
   f. Vision problem☐
   g. Hearing difficulty☐
   h. Other, specify_____
3. Examination findings

   MMSE_____ (*please complete the details on separate questionnaire for MMSE*)

   GOS_____ (*please complete the details on separate questionnaire for GOS)*

   Motor examination (check all that apply)

   a. Cranial nerve palsy ☐ (*Describe if any*)_____
   b. Hemiparesis ☐
   c. Hearing loss ☐
   d. Other, specify_____
4. Any other additional finding/remark_____

   _____
5. Complete discharge diagnosis_____

   _____

   If discharge diagnosis is other than BM, specify it and the date treatment started_____

   _____

Date of assessment_____

Completed by_____ signature_____

Checked by_____signature_____date_____

Please remind the patient to come after 3 months. There will be compensation for their expenses on that day.

Patient Contact: **Address**.....

Phone number.....

Initials: _____ MRN_____

Age: _____ Gender_____

*To be completed at **discharge***

Score Description

1. DEATH
2. PERSISTENT VEGETATIVE STATE

   Patient exhibits no obvious cortical function.
3. SEVERE DISABILITY (Conscious but disabled).

   Patient depends upon others for daily support due to mental or physical disability or both.
4. MODERATE DISABILITY (Disabled but independent).
   Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5. GOOD RECOVERY

   Resumption of normal activities even though there may be minor neurological or psychological deficits

TOTAL (1–5): _____

Date of assessment_____

Completed by_____ signature_____

Checked by_____signature_____date_____

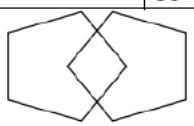
IMPROVING QUALITY OF CARE IN PATIENTS WITH ACUTE BATERIAL MENINGITIS AT JUSH | **MINI MENTAL STATE EXAMINATION (MMSE)**

JU – LMU LINK

Initials_____ MRN_____

Age_____ Gender_____ Date admitted_____

	Maximum Points	**Patient's score**
Orientation Name: season/date/day/month/year	5 (1 for each name)	
Name: hospital/floor/town/state/country	5 (1 for each name)	
Registration Identify three objects by name and ask patient to repeat	3 (1 for each object)	
Attention and calculation Serial 7s; subtract from 100 (e.g., 93–86–79–72–65)	5 (1 for each subtraction)	
Recall Recall the three objects presented earlier	3 (1 for each object)	
Language Name pencil and watch	2 (1 for each object)	
Repeat "No ifs, ands, or buts"	1	
Follow a 3-step command (e.g., "Take this paper, fold it in half, and place it on the table")	3 (1 for each command)	
Write "close your eyes" and ask patient to obey written command	1	
Ask patient to write a sentence	1	
Ask patient to copy a design (e.g., intersecting pentagons)	1	
Total	30	



Date of assessment_____

Completed by_____ signature_____

Checked by_____signature_____date_____

Please enter as much accurate information as possible!

IMPROVING QUALITY OF CARE IN PATIENTS WITH ACUTE BATERIAL MENINGITIS AT JUSH	Death report form

JU – LMU LINK

Initials _____ MRN_____

Age_____ Gender_____ Date admitted_____

_____

_____

Date and time of death_____

Time of death since admission, in hours_____ or days_____

Possible immediate cause of death

a. Brain herniation☐
b. Respiratory failure☐
c. Septic shock ☐
d. Multisystem organ failure☐
e. Other, specify_____

_____

Completed by_____ signature_____ date_____

Checked by_____ signature _____date_____

accuracy and completeness is essential for evidence based practice!

Annex – 3 Collection, processing, analysis and interpretation of CSF specimen

Collection of CSF – All patients suspected of having bacterial meningitis were screened for contradiction of lumbar puncture (LP). LP was differed in patient with any of the following conditions.

- ✓ Evidences of increased intracranial pressure (diplopia, abnormal pupillary responses, unilateral or bilateral motor posturing or papilledema)
- ✓ Focal neurological signs or seizures
- ✓ Local infection (in the area where LP would be performed)
- ✓ Severe thrombocytopenia ($<20 \times 10^9/L$)
- ✓ Cardio-pulmonary compromise
- ✓ Spinal deformity
- ✓ Lack of patient cooperation

As there was no CT scan facility at the hospital, the decision to do LP in patients in coma was left to the treating physician. However, due increased risk of herniation, LP was differed in patients with GCS of less than 5/15.

Lumbar puncture was done under possible aseptic condition for all patients with suspected BM to collect CSF specimen. This was done as soon as it was possible (before antibiotics administration). However, if the LP was not possible within an hour of presentation or consideration of diagnosis of BM, patient was given first dose of antibiotics and CSF collection was done within 24 hours of this. About 2-3 ml of CSF specimen was collected in two separate sterile tubes each. In case the tap was traumatic, the specimen was collected serially until the fluid became clear. The tubes were labelled as '1' and '2' based on their collection. The specimen was then sent to microbiology unit within 30 minutes of collection with special request form that contains demographic data, brief clinical description and whether patient has taken any prior antibiotics or not.

Processing of sample – Macroscopic appearance of CSF was observed and documented as crystal clear, turbid or bloody/traumatic.

The specimen from first tube was used for quantification of CSF glucose and protein levels. The second tube was used for cell count and microbiologic analysis. The specimen was centrifuged at 1500-3000 ×g for 20 minutes and the sediment was used to inoculate to culture media and for direct smear examination of gram-stain specimen. The supernatant was used for bacterial antigen detection.

Culture – The sediment of the centrifuged CSF was inoculated on to three plates as follows:

1. Blood agar plate (with Columbia 5% Sheep blood) incubated at 37°C in 5-10% CO_2
2. Chocolate agar plate incubated at 37°C in 5-10% CO_2
3. MacConkey agar incubated at 37°C

Inoculated primary plates were incubated for 72 hours. The plates were visually inspected daily for any growth for three days.

Gram-stain and microscopic evaluation – The CSF specimen was stained with gram-stain within 2 hours of its collection and from culture specimen if there was any growth to identify bacterial etiologies.

Interpretations of growth and gram-stain – Presumptive identification of three major causes of meningitis (*N. meningitidis*, *S. pneumoniae*, and *H. influenzae*) was made on the basis of growth and colony morphology on blood agar plate and chocolate agar plate, and a Gram stain of the organisms.

Blood agar	**Chocolate ager**	**Morphology (microscopic finding)**	**Interpretation**
+	+	Gram-positive diplococci in short chains	*S. pneumoniae*
+	+	Gram-negative diplococci	*N. meningitidis*
-	+	Pleomorphic gram-negative rods (coccobacilli) with random arrangements	*H. influenzae*

In case of growth on MacConkey agar; biochemical test for urease, indole, citrate, lysine, hydrogen sulphide and gas production was done to different the type of bacteria.

Antimicrobial susceptibility tests– all growths were tested for antibiotic susceptibility pattern using antibiotic discs that represented common antibiotics used in the setting. These included penicillin G, ampicillin, amoxicillin/clavulanic acid, ceftriaxone, gentamycin,

chloramphenicol, co-trimoxazole and ciprofloxacin. The result was interpreted as sensitive, intermediate and resistant according to the size of zone of inhibition which was interpreted based on European Committee on Antimicrobial Susceptibility Testing (EUCAST) Breakpoint tables for interpretation of MICs and zone diameters Version 4.0. It can found at: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/Breakpoint_table_v_4.0.pdf

Latex agglutination test (LAT) – CSF samples were tested for bacterial antigen detection by using the bacterial antigen kit (Wellcogen® Bacterial antigen kit, UK). It is a latex agglutination test to detect antigens of 5 groups of organisms:

1. Group B streptococcus (GBS)
2. Haemophillus influenzae type B (Hib)
3. Streptococcus pneumoniae
4. Neisseria meningitidis ACY W135
5. Neisseria meningitidis B/Escherichia coli K1

Other tests from CSF – Acid-fast bacilli staining and microscopic evaluation of the specimen was done for most of the patients. In all HIV patients, Indian ink staining of the specimen was done and the specimen was inoculated into Sabouraud dextrose agar for detection of fungal meningitis.

Reporting of the result – The report of laboratory findings was documented on a report form specifically prepared for this study. This is located on the second page of the request form.

CSF storage for future analysis – About 2ml of specimen from the second tube was immediately stored in -20^{0}C freezer after doing all the above tests. It was later transferred to -80^{0}C for possible further molecular analysis in the future.

Curriculum Vitae

PERSONAL INFORMATION

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Nationality:	Ethiopian
Date of birth:	14/02/1981
Gender:	Male

WORK EXPERIENCE

1. From June 9, 2010 until now

Position held	Consultant medical specialist (Internal medicine) and Associate Professor of Medicine
Employer	Jimma University Jimma, Ethiopia P.O.Box 378 Telephone: +251471111458 Fax: +251471118244 Website: http://www.ju.edu.et

2. From February 01, 2012 until March 31, 2014

Position held	Medical Director, Jimma University Specialized hospital
Employer	Jimma University

3. From December 13, 2006 to June 8, 2010

Position held	General medical practitioner/Medical Resident

Employer	Jimma University Specialized Hospital Jimma, Ethiopia P.O.Box 378 Telephone:+251471110867

EDUCATION AND TRAINING

1. From October 1, 2012 -

Type of training	PhD fellow
Principal subject covered	International health
Research project	Assessment of Treatment Strategies in Acute Bacterial Meningitis in Ethiopia
Name and address of the institution	Ludwig-Maximilian University Munich, Germany Website: http://www.international-health.uni-muenchen.de/index.html

2. **From January 1, 2011 to March 31, 2011**

Title of qualification awarded	Postgraduate diploma
Principal subject covered	Tropical medicine
Name and address of the institution	London School of Hygiene and Tropical Medicine Keppel Street London WC1E 7HT, UK Telephone +44(0)20 7636 8636

3. From January 2007 to January 2010

Title of qualification awarded	Certificate of Specialty
Principal subject covered	Internal Medicine
Name and address of the institution	Jimma University Jimma, Ethiopia P.O.Box 378 Telephone: +251471111458 Website: http://www.ju.edu.et

From September 2000 to November 2006

4. Title of qualification awarded	**Degree of doctor of medicine**
Principal subject covered	Medicine
Name and address of the institution	Jimma University

List of Publications

1. Yadesa TM, **Gudina EK**, Angamo MT. Antimicrobial Use-Related Problems and Predictors among Hospitalized Medical In-Patients in Southwest Ethiopia: Prospective Observational Study. PLoS One. 2015; 10(12):e0138385.
2. Desse TA, Eshetie TC, **Gudina EK**. Predictors and treatment outcome of hyperglycemic emergencies at Jimma University Specialized Hospital, southwest Ethiopia. BMC Res Notes. 2015; 8(1):553.
3. Jebena MG, Taha M, Nakajima M, Lemieux A, Lemessa F, Hoffman R, Tesfaye M, Belachew T, Workineh N, **Kebede E**, Gemechu T, Tariku Y, Segni H, Kolsteren P, al'Absi M. Household food insecurity and mental distress among pregnant women in Southwestern Ethiopia: a cross sectional study design. BMC Pregnancy Childbirth. 2015; 15(1):250.
4. Jaleta GN, **Gudina EK**, Getinet W. Left ventricular hypertrophy among black hypertensive patients: focusing on the efficacy of angiotensin converting enzyme inhibitors. BMC Res Notes. 2014; 7(1):45.
5. Bonsa F, **Gudina EK**, Hajito KW. Prevalence of Hypertension and Associated Factors in Bedele Town, Southwest Ethiopia. Ethiop J Health Sci. 2014; 24 (1):21-6.
6. **Gudina EK**, Michael Y and Sahilu A. Prevalence of hypertension and its risk factors in southwest Ethiopia: a hospital based cross-sectional survey. Integrated Blood Pressure Control. 2013; 6:111–117.
7. Shibiru T, **Gudina EK,** Habte B, Deribew A, Agonafer T. Survival patterns of patients on maintenance hemodialysis for end stage renal disease in Ethiopia: summary of 91 cases. BMC Nephrology. 2013; 14:127.
8. **Gudina EK** and Gudissa FG. Prevalence of tuberculosis in HIV in Ethiopia in early HAART era: retrospective analysis. The Pan African Medical Journal. 2013; 14:126.
9. **Gudina EK**, Tamiru S, Alemseged F and Ram R. Assessment of quality of care given to diabetic patients at Jimma University Specialized Hospital Diabetes Follow-up clinic, Jimma, Ethiopia. BMC Endocrine Disorders. 2011; 11:19.

Statement on Pre-release and Contribution

I declare and acknowledge that this PhD project is my original work and was conducted and coordinated by me; the writing, analysis and interpretations of the findings were done by me. My supervisors have supervised and contributed to design development and manuscript preparation. Other co-investigators in local universities have supervised data collection, cleaned the data and contributed to manuscript writing.

Part of this project has been submitted to journal of Tropical Medicine & International Health with title of 'Challenges of Bacterial Meningitis Case Management in Low income setting: an Experience from Ethiopia.' The peer review has been finalized and it is now been accepted for publication. The manuscript will be published online soon after copyediting, typesetting, pagination and proofreading process.

Affidavit

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Ethiopia

Country

I hereby declare, that the submitted thesis entitled

Assessment of Treatment Strategies in Acute Bacterial Meningitis in Ethiopia

is the result of my own work. I have only used the sources indicated and have not made unauthorised use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

The submitted thesis or parts thereof have not been presented as part of an examination degree to any other university.

I further declare that the electronic version of the submitted thesis is congruent with the printed version both in content and format.

Jimma, 30 April, 2016

Place, Date

Signature of PhD Candidate

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Esayas Kebede Gudina, MD