A RETROSPECTIVE STUDY ON THE PREVALENCE, ETIOLOGICAL AGENTS AND ASSOCIATED RISK FACTORS FOR NEONATAL MENINGITIS INFECTION FOR THE LAST TEN YEARS (2001- 2010) AT TIKUR ANBESSA SPECIALIZED HOSPITAL, ADDIS ABABA, ETHIOPIA

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Addis Ababa University

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ABBREVIATIONS

%	Percent
CDC	Center for disease control and prevention
CFRs	Case fatality rates
CNS	Central nervous system
CSF	Cerebral spinal fluid
DERC	Department ethical and review committee
G	gram
GBS	Group B *streptococcus*
HIb	*Haemophilus influenza* type B
HSV	Herpes simplex virus
IAP	Intra-partum antibiotic prophylaxis
IL-1	Interleukin one
IV	Intravenous
Kg	Kilo gram
LBW	Low birth weight
LP	Lumbar puncture
MBC	Minimum bactericidal concentration
Mg	Milligram
MICs	Minimum inhibitory concentration
MM^3	Millimeter cube
NICU	Neonatal Intensive care unit
PCR	Polymerase chain reaction
RDS	Respiratory distress syndrome
Spp	Species
TASH	Tikur Anbessa Specialized Hospital
TNF-a	Tumor necrosis factor alpha
VLBW	Very low birth weight
Vs	Versus
WBC	White blood cells

ABSTRACT

Background: - Meningitis occurs more commonly during the first month of life (between birth and the first 28 days of life) than during any other subsequent period and it is associated with high morbidity and mortality. The causes of bacterial meningitis in the neonatal period are generally distinct from those in older infants and children and reflect the maternal gastrointestinal and genitourinary flora and the environment to which the infant is exposed. Data on the recent relative magnitude of the neonatal meningitis infection and associated risk factors is insufficient in Ethiopia.

Objective: - The aim of this study was to determine the prevalence, etiologic agents for neonatal meningitis infection and associated risk factors in Tikur Anbessa Specialized Hospital.

Methods: - This is a retrospective analysis of 2510 CSF and blood specimens submitted to the bacteriology laboratory of Tikur Anbessa Specialized Hospital for culture in the period between Jan, 2001 and Dec, 2010. The study was done from April, 15- June, 2011.

Result: - For this retrospective study data were obtain from 1321 males and 1189 females making male to female ratio 1.1:1. Of 2510 total culture 1321(52.63 %%) were from blood and 1189(47.37%) were from CSF. The causative agent had been isolated (414) showing an isolation rate of (16.49%) of the total 2510 meningitis suspected cases; 358(27.10%) were isolated from blood, while 56(4.71%) have been isolated from CSF culture. The numbers of bacterial meningitis cases in each year from 2001 to 2010 were 41, 18, 16,50,54,46,44,45,40 and 56, respectively and the positive isolation rates in the same year were 13.6%, 14.6%, 17.0%, 25.1%, 20.8%, 26.1%, 15.5%, 15.5%, 12.8% and 12.6% respectively. 56 (13.53%) of bacterial pathogen were isolated only in the year 2010. Higher peak had been observed from the year 2004 to 2006. Of 414 positive for neonatal bacterial meningitis cases; the most common isolated pathogens were *Coagulase-negative-staph* 148(35.75%), *S.aureus* 65(15.70%), *K.pneumoniae* 50(12.08%), *Acinetobacter* 45(10.87%), *E.coli* 28 (6.76%). *Coagulase-negative-staphylococcus* was the predominant pathogen accounting for 148(35.75%) of all cases. Whereas *S.aureus* and *K.pneumoniae* accounted for 65(15.70%), 50(12.08%) respectively: More than 50% of the pathogens were isolated from neonates having preterm birth and LBW. Of 75 positive cases that have been properly treated; 66(88%) were given a combination of ampicillin and gentamycin.

Conclusion:-*Coagulase –negative-staphylococcus* remains the major causative agent of neonatal bacterial meningitis infection in the study area. More than 50% were isolated from neonates having preterm birth and LBW; hence, preterm birth and LBW were major risk factors for neonatal bacterial meningitis infections.

Keywords:-Neonates, bacterial meningitis, *coagulase-negative-staphylococcus*

1. INTRODUCTION

1.1. Background

Meningitis is a very serious infection of the meninges that surround the brain and spinal cord. It is usually caused by viral, bacteria or fungal pathogens. Bacterial meningitis is a severe, potentially life-threatening infection that is associated with high rates of morbidity and significant disability in survivors and can be quit severe and may result in brain damage, hearing loss, or learning disability and death if not treated early. Despite advance in vaccines development and chemoprophylaxis, bacterial meningitis remains a common disease worldwide. The disease is more common in developing countries (Andargachew *e t al.,* 2005).

Meningitis can affect anyone in any age group, from the newborn to the elderly. From its recognition in 1805 until the early 20th century, bacterial meningitis was virtually uniformly fatal. Until recent years, up to 50% of patients who survived the acute infection would be left with permanent sequelae such as mental retardation and hearing loss. Over the past several years, there has been a striking shift in the demography of meningitis. In 1986, the median age of a patient with meningitis was 15 months, as compared with 25 years in 1995. Before the widespread use of the conjugated *H. influenza* type B (Hib) vaccine in 1990*, H.influenzae* type b meningitis developed in nearly 1 in 200 children<5 years old, and almost 70% of the cases of meningitis in children<5 were due to *H.influenzae* (Greenwood, 2006).

It appears that recent epidemic meningitis is a relatively phenomenon. The first recorded major outbreak occurred in Geneva in 1805. Several other epidemics in Europe and the United States were described shortly afterward, and the first report of an epidemic in Africa appeared in 1840. African epidemics became much more common in the 20th century, starting with a major epidemic sweeping Nigeria and Ghana in 1905–1908 (Medical news, 2010).

The "Meningitis Belt" is an area in sub-Saharan Africa which stretches from Senegal in the west to Ethiopia in the east in which large epidemics of *Meningococcal meningitides* occur (this largely coincides with the Sahel region). It contains an estimated total population of 300 million people. The largest epidemic outbreak was in 1996, when over 250, 000 cases occurred and 25,000 people died as a consequence of the diseases. Africa experiences a disproportionately large burden of meningitis due to its young population, epidemics in the meningitis belt and high rates of endemic diseases. The incidence and

CFRs associated with pediatric HIb and *Pneumococcal meningitis* were highest in Africa compared in a recent global review. In addition Africa is the only region with cyclic epidemics of meningitis that affect persons of all ages, with attack rates of ranging from 100 to 800 per 100,000 populations. Epidemics of meningitis are mostly associated with *meningococcal*, but there is some evidence that increases in *Pneumococcal meningitis* cases occur in parallel during, the hot and dry season (Meenakshi *et al*., 2009).

Bacterial meningitis is contagious. The bacteria are spread through the exchange of respiratory and throat secretions (i.e., coughing, kissing). Fortunately, none of the bacteria that cause meningitis are as contagious as things like the common cold or the flu. Also, the bacteria are not spread by casual contact or by simply breathing the air where a person with meningitis has been. Sometimes the bacteria that cause meningitis have spread to other people who have had close or prolonged contact with a patient with meningitis caused by *N. meningitidis* or *H. influenzae* serotype b. People in the same household or daycare center or anyone with direct contact with a patient's oral secretions (such as a boyfriend or girlfriend) would be considered at increased risk of getting the infection. People who qualify as close contacts of a person with meningitis caused by *N. meningitidis* should receive antibiotics to prevent them from getting the disease (CDC, 2009).

Meningitis occurs more commonly during the first month of life than during any other subsequent period and it is associated with high morbidity and mortality. The incidence of neonatal meningitis in western countries varies from 0.2-0.5 cases per 1000 live births but much higher rates of 1.1-1.9 per 1000 have been reported from developing countries (Laving *et al.,* 2003).

The neonatal meningitis is an illness characterized as a result of infection and inflammation of the meninges and it typically happens between birth and the first 28 days of life. The bacterial infection is more common during the first month after birth compared to other stages of newborns. It has an incidence that varies from 0.22 to 2.66/1,000 newborns in different countries and it tends to be common in developing countries (Luzia *et al*., 2007).

During the neonatal period, the illness has special characteristics. The etiology, the clinical symptoms and the mortality appear too different from the observed in older children. The mortality varies based on the treatment, with survival rates of 17% to 29% and with complications rates of 15% to 68 %. Although there have been medical advances of medicines and preventive medicine, the incidence of newborn bacterial meningitis for the last 30 years has been barely affected (Luzia *et al*., 2007).

1.2. Statement of the Problem

Bacterial meningitis is a severe, potentially threatening infection that is associated with high rates of morbidity and significant disability in survivors. In recent years, despite improvement in antimicrobial therapy and intensive care support, overall mortality rates related to bacterial meningitis of around 20% to 25% have been reported by major centers (Marc and Nigel, 2008). In the neonatal period, Group B *streptococci* and gram-negative bacilli use most bacterial meningitis. *HIb, N. meningitidis* and *S. pneumoniae* were the most common causative organisms of bacterial meningitis worldwide in children (Hye *et al.,* 2010).

Bacterial meningitis infections resulting in 170,000 deaths worldwide each year; Young children are particularly vulnerable to bacterial meningitis, and when exposed poor outcomes may occur due to the immunity of their immune systems. Two-thirds of meningitis deaths in low income countries occur among children under 15years of age (Meenakshi *et al*., 2009).

Africa children have some of the highest rates of bacterial meningitis in the world. Bacterial meningitis in Africa is associated with high cases fatality and frequent neuropsychological sequelae. Neonatal meningitis remains a serious problem with the high mortality rates of 60%. In no other age group is meningitis more common than in the new born with an incidence of 0.4/1000 live births (Bell *et al*., 1989).

Both endemic and epidemic forms of meningococcal meningitis has affected Ethiopia for a number of years, for instance outbreaks and epidemics have been reported in 1935 and 1940 (Habte, 1984) and the 1950s, 1964, 1976 1977, 1981 to 1983, and 1988 to 1989. Prior to 1988, the majority of epidemics cases occurred in the north, the northwest, and parts of the central regions of Ethiopia, which lie within the eastern end of the traditional belt of Africa (Norheim, 2006, Mengistu, 2003).

Epidemics were also reported in Ethiopia in the years 2001 to 2003. The numbers of cases in each year from 2000 to 2003 were 855, 6,266, 2,329 and 3,540 respectively and the case fatality rates (CFRs) in the same year were 2.2, 5.0, 5.0 and 4.7 respectively (Norheim, 2006).

Thus, the aim of this study is to determine the prevalence, etiological agents and associated risk factors for neonatal meningitis infection and to give this information to the health institutions and policy makers to support decision making that can improve the functioning of the health systems. The newborns that will be included in this study should have neonatal meningitis infections within the neonatal period (0-28 days of life).

1.3. Literature Review

Epidemiology of neonatal bacterial meningitis infections

A retrospective survey of neonatal meningitis occurring in Australia was conducted from Jan, 1987 to Dec, 1989. Data were obtained from Medical Records and Microbiology Departments of Hospitals with neonatal nurseries. A Total of 116 infants < 6 weeks of age with bacterial or fungal meningitis were registered and the incidence was 0.17/1000 live births. Traditional neonatal pathogens were responsible for 60% of cases (group B *streptococcus*, 35%; *E.coli*, 22%), childhood meningeal pathogens for 10% and opportunistic pathogens for 30%. Risk factors for meningitis, including prematurity, were more common among those with meningitis due to *E.coli* or opportunistic pathogens than among those with infections due to group B *streptococci*, *L.monocytogenes* or the childhood pathogens (46/60 V. 11/55; P <0.0001). Meningitis was more likely due to Gram-negative bacteria in premature infants than in full-term infants (19/30 v.20/86; p=0.0002). The overall mortality was 26% but was higher in extremely premature infants (6/9 v.24 107; p=0.009) (Francis and Gilbert, 1992).

A 3-year retrospective study was conducted from 1988-1990 at the Mount Hope Women‟s Hospital, Trinidad, West Indies to report the experience with neonatal meningitis at the Neonatal Intensive Care Unit. Neonates were included in the study if organisms were culture from the cerebrospinal fluid (CSF) and /or if there was a pleocytosis (> or=100/mm^3) in the CSF. There were 49 neonates with meningitis out of a total of 17,048 live born infants during the 3-year period to give an overall incidence of 2.87/1000 live birth. There were 34 male (63%) with mean birth weight of 2389g. Antenatal risks included preterm delivery (50%), prolonged rupture of amniotic membranes (37%). Association maternal conditions included hypertension and ante-partum hemorrhage (9%). In contrast of other reported studies, there was early onset of the condition (mean age at presentation was 4 days) and the commonest organisms found was Group b *streptococcus* while the least common were Gram- negative organisms (Ali, 1995).

During the period Jan, 1980 to Dec, 1990(11 years) a retrospective study of patients with bacterial meningitis who were admitted to Bangkok Children‟s Hospital, Thailand was carried out. There were 618 patients with 77 cases (12.5%) occurring below the age of one month (neonatal meningitis), and 541 cases (87.5%) between one month to 15 years (childhood meningitis). *Pseudomonas aeroginosa* was the most common pathogenic organism (16.9%) in neonatal meningitis; other causative agents in this age group included *K. pneumoniae* (13.0%) group B *streptococcus* (11.7%), *E.coli* and *Enterobacter* spp(10.4%). In childhood meningitis, *H. influenzae* was the most common causative organism (42.3%), and followed by *S.pneumoniae*(22.2%) and *salmonella* Spp(12.4%). S*almonella* meningitis occurred exclusively in infants, 87% of them were under six months, and 13% of them developed relapsing meningitis. The overall fatalities during 1980-1990 were 45.4% and 17.3% for neonatal meningitis and childhood meningitis, respectively. The fatalities of the two age group decline 1987-1990 to 26.3% and 11.4% respectively (Chotpitayasunondh, 1994)

Babies admitted from 1992 to 1995 in the special Care Baby Unit of the University of Maiduguri Teaching Hospital, Nigeria, with bacterial meningitis were studied retrospectively. Neonatal bacterial meningitis was confirmed if the CSF microbiological, chemical, immunological and clinical criteria were satisfied.69 cases of neonatal bacterial meningitis were encountered, (25 were early-onset, and 44 late-onset); the incidence was 6.5/1000 live births. 22 positive CSF cultures were grown in early-onset meningitis; and 28 in late-onset diseases. LBW showed higher risk of bacterial meningitis and it was significantly more likely in the preterm(X^2=24.19, P=0.000001).Gram- negative pathogens were more isolated (28/50, 56%); *E.coli* (11) being the commonest, while of the Gram-positive pathogens *S. aureus* was most predominant overall (13/50). Concomitant blood culture was positive in 39/50 (78%), inclusive of all 22"definite" early-onset disease. *N.meningitidis* (2) and *H.influenzae* (2), contributing 0.6 and 2.2 per 1000 live births and admissions respectively. Overall mortality was 24.6% (Airede *et al*., 2008).

A prospective multicenter study was conducted to assess the incidence, etiology, risk factors and outcomes of vertically transmitted and nosocomial meningitis in a neonates over a 2 years period between Jan, 1, 1997 and Dec, 31, 1998 in the Neonatology Department of 28 acute- care Hospitals in Spain. Bacterial meningitis was considered confirmed when CSF was positive, virus or fungi, probable when CSF culture was negative but blood culture was positive, and unconfirmed when both cultures were negative. During the study period, 151 cases of meningitis were diagnosed. Transmission was vertical in 84 cases and nosocomial in 67. The incidence of vertically transmitted meningitis was 0.51/1000 live births, and was significantly higher in VLBW infants. Confirmed bacterial meningitis was diagnosed in 66 patients (78.6%). No risk factors were identified in 46.4% of infants. GBS was isolated in 48.5% of cases of confirmed meningitis and *E. coli* was isolated in 18.2%. In 69.7% of cases the results of blood culture were in agreement with those of CSF culture. The overall mortality rate was 8.3%; mortality was significantly higher in VLBW infants (33.3% Vs 4.2% in infants weighing 1,500g).the incidence of meningitis of nosocomial transmission was 0.2% of admissions and was more frequent in VLBW infants.

E.coli was isolated in 26.5% of cases of nosocomial meningitis and *Staphylococcus epidermidis* was isolated in 24.5%. In 55% of patients the results of blood culture agreed with those of CSF culture. The overall mortality rate was 19.4% (Grupo de Hospitals Castrillo, 2002).

Another retrospective study was conducted in Mexico from Jan, 1990-july 1995 to determine incidence, etiologic agents and clinical manifestations of bacterial meningitis in patients hospitalized in the newborn ward at the infants Hospital and establish the incidence of meningitis in newborns admitted with RDS and determine how often blood cultures are negative in bacterial meningitis. There were 959 admissions in the NICU. The overall incidence of bacterial meningitis was 32.3/1000 admissions; however, among 170 patients with RDS, meningitis was detected in one (5.9/1000 RDS patients). Of the 31 patients with bacterial meningitis, 10 were preterm and 21 term. In the CSF isolates, there was a predominance of Gram- negative rods (n: 19; 61%). Clinical findings associated to meningitis were non-specific and there were no difference between preterm and term infants. From 31 patients, 19 had negative blood cultures at the time of diagnosis (61%). Mortality associated to bacterial meningitis was 40% and 23%, for preterm and term respectively (Rios, 1998).

A two and a half year prospective study of neonatal meningitis in the two main referral Hospitals in Northern Jordan (Princess Badia"a and Prince Rashid Military Hospitals) was carried out during the period between Jan, 1992 and July 1994 to determine the clinical and particular characteristics of meningitis in the new born. During the two and half year study period there were 47,669 live births in the Catchment areas of the two Hospitals and 53 infants with neonatal meningitis were seen, and the incidence was 1.1 per 1000 live births. 42 patients had micro-organisms cultured from their CSF, whilst the remaining 11 has positive blood cultures and significant pleocytosis despite their CSF cultures being sterile. 29 were boys and 24 were girls with a male to female ratio of 1.2:1. There were 24 preterm and /or LBW infants, whilst the rest were born at term. The mean age at presentation was 7 days (range 1-28).15 neonates were seen within 48h of birth(early-onset), the remaining 38 patients presenting more than 48h after birth(late-onset).gram-negative organisms were isolated most frequently(87%) with a predominance of *Klebsiella* Spp(40%). 17 of the neonates died and 22 without any residual disability. Rates of mortality and neurological sequelae were higher among the preterm/LBW patients when compared to full term/normal birth weight group (38% v 28%) and (53% v 29%) respectively(Doaud *et al*, .1996).

There was one retrospective study conducted in Addis Ababa University Teaching Hospital, Ethiopia. In population-based retrospective study of neonatal meningitis, 55 cases were identified over a period of 10 years. The prevalence of meningitis for preterm and term newborns were 3.66 and 0.97 per 1000 live birth, respectively (22/6465 Vs 33/36638; $p<0.01$). The overall prevalence was 1.37 per 1000 live births. 22(40%) babies with meningitis died, more preterm than term (13/22 Vs 9/33; $p<0.05$). known maternal risk factors for neonatal meningitis were observed in 15 (27%) babies. The risk factors were more common in preterm than in term newborns (10/22 Vs 5/33; $p<0.05$). The common causative organisms were *Klebsiella pneumoniae*, *E.coli* and *enterobacter* Spp. which together accounted for 67% of all CSF isolates. These organism were evenly distributed between early and late-onset meningitis, and among term and preterm newborns.7 of 33(21%) of the surviving newborns developed neurological complications (Gebremariam, 1998).

Most Common Causative Agents for Neonatal Meningitis Infections

The causes of bacterial meningitis in the neonatal period (0-28 days) are generally distinct from those in older infants and children. The bacteria that cause the meningitis in newborns reflect the maternal gastrointestinal and genitourinary flora and the environment to which the infant is exposed (Robert *et al.,* 2007). Neonatal meningitis represents fewer than 10% of cases of meningitis, but more than 50% of meningitis deaths (Samuel, 1996). Group B *streptococci* and *E.coli* strains account for approximately two thirds of all cases of neonatal meningitis, while bacteria that typically account for meningitis in older age groups (*HIb*, *N. meningitides*, and *S. pneumoniae*) are infrequent causes of meningitis in the neonatal population (Kimberlin, 2002). The main bacterial pathogens causing meningitis beyond the neonatal period are *S.pneumoniae*, *HIb* and *N. meningitidis*. *Pneumococcal* meningitis is associated with the highest case fatality ratios globally. In Africa, pneumococcal meningitis CFRs attains 45% compared to 29% for HIb meningitis and 8% for meningococcal meningitis (Meenakshi *et al*., 2009). The most common cause of bacterial meningitis in children 2 months to 12 years of age in the United States is *N. meningitis*. Bacterial meningitis caused by *S.pneumoniae* and *HIb* has become much less common in developed countries since the introduction of universal immunization against these pathogens beginning at 2 months of age (Robert *et al.,* 2007).

The microorganisms causing neonatal meningitis not only vary between different countries, but show temporal changes within the same country. In developed countries, infection with gram-negative bacilli accounts for 30-40% of meningitis case. *E.coli* is the most common organisms isolated (50%) of all gram-negative isolates, followed by *K. pneumoniae* (Klein, 2000). In developing countries, gram-negative bacteria are the most common causes, and *Klebsiella spp*. and/ *or E.coli* are the predominant causative agents. The disease is often more severe with gram-negative bacteria than with gram-positive bacteria, with higher rates of both mortality and morbidity. The CFR in several recent reports from developed countries has ranged from 3% to 13% as compared to 25% to 30% reported 15-20 years ago, also less developed countries still reported rates of 30%-40% (Mohammad *et al.,* 2010).

Early onset meningitis is more likely to be caused by Group B *streptococcus*, *E.coli*, and *L. monocytogenes*, while late onset meningitis may be caused by other gram- negative organisms as well as *Staphylococcal* Spp. Unfortunately most case series on neonatal meningitis do not distinguish cases according to their age at onset (Heath *et al*., 2003).

Risk Factors for Neonatal Meningitis Infections

The development of sepsis and meningitis in the neonates depends on several risk factors in both the infants and the mother, as well as on the virulence of the pathogen. Prematurity(<37weeks gestation), prolonged rupture of membranes(walls of the bag that hold the developing foetus/infant and the fluid that surrounds the foetus during pregnancy) more than 18 hours before birth, and low birth weight but also prenatal, intrauterine infections and maternal urinary tract infections are strongly associated with neonatal meningitis infections. The mode of infection of the neonates may be either hematogenous (transplacental) or directly through aspiration or inhalation of the pathogen. An early onset of neonatal bacterial meningitis indicates vertical transmission, whereas later onset is mainly caused by nosocomial infection (Bozena *et al.,* 2005).

Neonates are at greater risk of sepsis and meningitis than other age groups because of deficiencies in humoral and cellular immunity and phagocytic function, lower integrity of barriers, and immature defense mechanism. Infants younger than 32 weeks‟ gestational age receive little of the maternal immunoglobulin received by full-term infants. Inefficiency in the neonates‟ alternative complement pathway compromises their defense against encapsulated bacteria (David, 2010).

Pathogenesis (Mechanisms) of neonatal Meningitis Infections

Bacteria from the maternal genital tract colonize the neonate after rupture of membranes, and specific bacteria, such as group B *streptococci*, enteric gram- negative rods, and *L.monocytogenes,* can reach the fetus transplacentally and cause infection during vaginal delivery. Babies may also be exposed to certain bacteria (such as *pneumococcus*, the *meningococcus* and *HIb*, through respiratory-borne secretions but very few become ill. Furthermore, newborns can also acquire bacteria pathogens from their surroundings, and several host factors facilitate a predisposition to bacterial sepsis and meningitis. Bacteria reach the meninges, via the bloodstream and cause inflammation. After reaching the CNS, bacteria spread from the longitudinal and lateral sinuses to the meninges, the choroid plexus, and the ventricles (Martha, 2010). IL-1 and TNF-α also mediate local inflammatory reaction by inducing phospholipase A_2 activity; initiating the production of platelet-activating factors and arachidonic acid pathway. This process results in production of prostaglandins, thromboxanes, and leukotrienes. By activating adhesion- promoting receptors on endothelial cells, these cytokines result in attraction of leukocytes, and then release of proteolytic enzymes from the leukocytes causes alteration of blood-brain permeability, activation of coagulation cascade, brain edema, and tissue damage (Martha, 2010).

Sing and Symptoms of Meningitis

Clinical Features of Meningitis Infections: - The early signs and symptoms of meningitis are very non-specific and indistinguishable from those of septicemia and other non-infective causes such as birth asphyxia, respiratory distress syndrome and hypoglycemia amongst others. A high index of suspicion is therefore necessary and laboratory support essential to make a diagnosis and offer appropriate treatment. Since blood cultures have been reported negative in up to 50% of cases of neonatal meningitis, examination of CSF is the only confirmatory method of establishing a diagnosis (Laving *et al.,* 2003).

The primary clinical manifestations of meningitis are headache, fever and nuchal rigidity (stiffness of the neck on passive forward flexion due to stretching of the inflamed meninges). Meningeal inflammation may also cause some degree of obtundation (reduced consciousness), and seizures are common in children (Samuel, 1996).

The sign commonly associated with meningitis are photophobia (inability to tolerate bright light), phonophobia (inability to tolerate loud noise), irritability and delirium (in small children) and seizures (20-40% of cases), in infants (0-6 months) swelling of the fontanel (soft spot) may be present. The most common symptoms of neonatal meningitis may include; feeding poorly or refusing to feed, irritability, trouble breathing, Bulging fonatelle(the soft at the top of the head), diarrhea ,and feeling too warm or too cold (Jean, 2009).

Early Complications of Meningitis Infections: - In children there are several potential disabilities which result from damage to the nervous system. These include sensorineural hearing loss, epilepsy, and diffuse brain swelling hydrocephalus, cerebral vein thrombosis, intra cerebral bleeding and cerebral palsy. In childhood acute bacterial meningitis deafness is the most common serious complication. Sensorineural hearing loss often develops during first few days of the illness as a result of inner ear dysfunction, but permanent deafness is rare and can be prevented by prompt treatment of meningitis (Richardson *et al*., 1997). Regardless of etiology, meningitis in neonates can progress rapidly to serious complications. These include cerebral edema, hydrocephalus, hemorrhage, ventriculitis (especially with bacterial infection), abscess formation, and cerebral infraction (Pong and Bradley, 1999).

Diagnosis of Meningitis Infections

Clinical diagnosis: When evaluating neonates for meningitis, the following points should be consider (1) be vigilant for maternal infection „set-ups" including prolonged rupture of membranes, fever, and chorioamnionitis, remembering that symptomatic maternal infection is always a possibility even with screening: (2) early-onset and let onset bacterial infections have distractive clinical courses, and (3) in HSV infection, the presence of skin lesions in a meningitic neonate are the exception rather than the rule(Volpe, 2008).

- **Bacterial Meningitis, Early Onset: -** Symptoms appearing in the first 48 hours of life are referable prematurity to systemic illness rather than meningitis. These include temperature instability, episodes of apnea or bradycardia, hypotension, feeding difficulty, hepatic dysfunction, and irritability alternating with lethargy. Respiratory symptoms can become prominent within hours of birth in GBS infection; however, the symptom complex also is seen with infection by *E. coli* species (Volpe, 2008).
- **Bacterial Meningitis, Late Onset:-** Late-onset bacterial meningitis (symptoms onset beyond 48 hours of life) is more likely to be associated with neurological symptoms. Most commonly seen are stupor and irritability, which Volpe (2008) describes in more than 75% of affected neonates. Between 25% and 50% of neonates will exhibit the following neurological signs; bulging anterior fontanel; extensor posturing/opisthotonus; focal cerebral signs including gaze deviation and hemiparesis; cranial nerve palsies. Nuchal rigidity perse is the least common neurologic sign in neonatal bacterial meningitis, occurring in fewer than 25% of affected neonates (David, 2010).

Laboratory Diagnosis

CSF and Blood Cultures:- Suspected bacterial meningitis infection is confirmed often, but not uniformly, by positive results of cultures of CSF. About 15-30% of neonates with negative blood cultures have positive CSF cultures depending on the population studied. CSF culture should be obtained in all symptomatic infants (Garges *et al.,* 2006). Blood cultures also should be performed in all patients with suspected meningitis. Blood culture reveals the responsible bacteria in up to 80-90 % of causes of meningitis (Robert *et al.,* 2007). The diagnosis of acute bacterial meningitis confirmed by analysis of the

CSF which typically reveals microorganisms on Gram stain and culture, a neutrophilic pleocytosis elevated protein, and reduced glucose concentrations. Lumbar puncture should be performed when bacterial meningitis is suspected. The CSF leukocytes count in bacterial meningitis usually is evaluated to >1,000/mm^3 and, typically, there is a neutrophilic predominance (75-95%). Turbid CSF is presented when the CSF leukocyte count exceeds 200-400/mm^3. Normal healthy neonates may have as many as 30 leukocytes/mm^3 (usually<10), but older children without viral or bacterial meningitis have <5 leukocytes/mm^3 in the CSF; in both age groups there is predominance of lymphocytes or monocytes (Robert *et al.,* 2007).

Polymerase Chain Reaction (PCR):- Polymerase chain reaction assay is a powerful diagnostic tool with excellent sensitivity and specificity. It permits identifications of group B streptococcus antigen in urine or in CSF, and it is the criterion standard for identification of HSV and enteroviral infection in CSF. PCR for HSV is 71-100% sensitivity but 98-99% specific in neonates. As PCR becomes more widely available, recognition of enteroviral infections has increased (David, 2010).

Latex Particle Agglutination:- Rapid screening is available with latex particle agglutination test of urine, which can be performed for Group B *streptococcus, E.coli*, and *Streptococcus pneumoniae*. Unfortunately, the presence of Group B *streptococcus* antigen does not prove invasive disease (David, 2010).

Treatment and Prevention of Meningitis Infections

Antibiotic Therapy:-Appropriate antibiotic therapy is a critical aspect of management. Antibiotic choice is empirical, based on age at onset, likely pathogens, and antibiotic susceptibility patterns, with a focus on GBS, *E.coli*, other gram-negative organisms, and *L.monocytogenes*. Antibiotics are modified according to culture and antibiotic susceptibility result. Delay CSF sterilization is a particular feature of gram negative meningitis and may in parts account for its higher mortality compared with group B streptococcus. CSF culture is dependent on achieving bactericidal antibiotic concentration within the CSF. This will be influenced by the dose of antibiotic that can be administered safely, the penetration of antibiotics into the CSF, and the minimum bactericidal concentration of the infected organisms (Lutsar *et al*., 1998).

Group *B streptococcus*:- Group B *streptococcus* is uniformly susceptible to penicillin, ampicillin and cephalosporin. It is usually resistance to aminoglycosides. It is seems prudent to use the narrower spectrum agent, penicillin, in order to minimize any potential impact on antibiotic resistance among other pathogens. Because group B *streptococcus* has an MBC tenfold higher than Group *A streptococcus*, and the inoculums in the CSF of neonates with meningitis is generally much higher than that of older infants and children with meningitis, it is recommended that large doses of antibiotics are administered. For ampicillin the recommended dose is up to 300mg/kg/daily divided 8 hourly if <7 days of age or 4-6 hours if >7 days of age. Penicillin or ampicillin are initially combined with gentamycin 4mg/kg/dose daily (32-35 weeks gestation) or 5 mg/kg/dose daily (>35 weeks gestation). The recommended doses of cefotaxime are 50mg/kg/dose 12 hours (<7days,) 8 hourly (7-21days), and 6-8 hourly (>21days) (Heath *et al.,* 2003).

Gram- negative enteric bacteria:-The bacteria in this group include *E.coli, klebshella, enterobacter, ctrobacter, salmonella, proteus, pseudomonas,* and *serrstia*. The combination of ampicillin and amonoglycoside has been used for the treatment of gram- negative meningitis for several decades. However, these gram-negative organisms are frequently resistance to ampicillin; CSF amino glycoside concentration is often minimally above their MICs, CSF culture remains positive longer than with GBS meningitis. This lead to consideration of other therapeutic strategies such as intrathecal and intraventricular administration of antibiotics such as gentamicin, while certain infants with obstructive ventriculitis complicating gram negative meningitis may require administration of intraventricular amino glycoside to assist in sterilization of the CSF, this therapy is not recommended routinely. The introduction of cefotaxime has provided an attractive option for therapy of gram negative meningitis. This is based on the lower MBCs of gram negative bacteria to cefotaxime compared to penicillin and amino glycosides and the high CSF concentration that can be safely achieved. However for reasons stated above, cefotaxime (or ceftazidime in the case of *Pseudomonas aeruginosa*) is recommended for therapy in suspected neonatal gram negative meningitis in combination with an amino glycoside, usually gentamicin(Heath *et al.,*2003).

***Listeria Monocytogenes:* -** *L.monocytogenes* is not susceptible to cephalosporin. Ampicillin is the mainstay of therapy, and the combination of ampicillin and gentamicin is synergistic in vitro and provide more rapid bacterial clearance in animal models of infection. Thus this combination is favoured for initial therapy, with cessation of the amino glycoside when the CSF has been sterilisated and the patient has improved clinically (Heath *et al*., 2003).

***Streptococcus pneumonae*: -** While penicillin resistance does occur and may be increasing in incidence and empirical combination of penicillin or ampicillin and cefotaxime is satisfactory. Once *S.pneumoniae* is identified and susceptibility testing results available, therapy may be completed with either agent alone. *S.pneumoniae* (*pneumococcus*) can usually be treated with a 2-week course of IV antibiotics; Penicillin sensitive (penicillin G), Penicillin-intermediate (ceftriaxone or cefotaxime) and Penicillin-resistance (ceftriaxone or cefotaxime +vancomycin) (Heath *et al*., 2003).

Vaccination and prophylaxis

Vaccination and antibiotic prophylaxis of susceptible at-risk contacts represent the two available means of reducing the likelihood of bacterial meningitis. The availability and application of each of these approaches depends on the specific isolating bacteria (Robert *et al.,* 2007). Currently, conventional therapy with ampicillin and an amino-glycoside should be used as initial empirical therapy for neonatal meningitis. Once the pathogen has been identified and the susceptibilities determined, the most appropriate antibiotic or combination of antibiotics can be selected (McCracken, 1984). Currently the best means of neonatal Group B *streptococcus* prevention is the use of maternal intra-partum antibiotic prophylaxis to prevent early onset Group B *streptococcus* disease. Judicious antibiotic use, including the use of narrow spectrum antibiotics, stopping antibiotics when cultures are negative and not using antibiotics to treat colonization or as prophylaxis, as well as enforcement of hand hygiene policies, are obvious prevention strategies for neonatal remaining in the hospital; Maternal vaccination against Group B *streptococcus* offers the best hope of protection against both early and late onset Group B *streptococcus* meningitis (Heath *et al*., 2003).

1.4. Significance of the Study

Meningitis is a serious life threatening infection that the incidence increases in all age groups. Particularly bacterial meningitis is a serious, disabling and potentially fatal infection resulting in 170,000 deaths worldwide in each year (Meenakshi *et al*., 2009). African children have some of the highest rates of bacterial meningitis in the world. This highest rate in Africa is associated with high case fatality and frequent neuropsychological sequelae. Many neonatal meningitis related studies have conducted in different countries especially in developed countries but less in developing countries.

Therefore, the result of this retrospective study will provide information about the prevalence, etiological agents and associated risk factors for neonatal bacterial meningitis infection. The result of this study gives data for the health institutions, for their research and to take any measurement to prevent and control neonatal bacterial meningitis transmission thereby decreasing the morbidity of this dread disease. The study will also serve as an input for further reviews and neonatal bacterial meningitis related studies.

2. OBJECTIVE OF THE STUDY

2.1. General Objective

- To study the prevalence, etiological agents and associated risk factors for neonatal bacterial meningitis infection in neonates who had attended at Tikur Anbessa Specialized Hospital in the last ten years (January, 2001 to December, 2010).

2.1.1. Specific Objective

- To assess the etiological agents of neonatal bacterial meningitis infection
- To determine prevalence of neonatal bacterial meningitis infection
- To assess the associated risk factors of neonatal bacterial meningitis infection
- To evaluate the measurement under taken for neonatal bacterial meningitis infection in Tikur Anbessa Specialized Hospital

3. MATERIALS AND METHODS

3.1. Study Design

This retrospective study was conducted from April to June, 2011 to analyze the recorded data for neonatal bacterial meningitis infection cases available in Tikur Anbessa Specialized Hospital for the last ten years (January, 2001 to December 2010).

3.2. Study Area and Period

The study was conducted in Tikur Anbessa Specialized Hospital in Addis Ababa, Ethiopia. Addis Ababa has ten sub-cities. The City lies at an altitude of 7,546 feet (2,300metres) and is a grassland biome, located at 9^{0}1‘‘48”N38^{0}44‘‘24’E9.03^{0}N38.74^{0}E. It is the largest and capital City of Ethiopia with a population of 3,384,569 according to the 2007 population census (Said *et al.*, 2002). Tikur Anbessa Specialized Hospital is the largest referral Hospital in which patients referred by different Hospitals of Addis Ababa and anywhere in the country are examined. Relevant data was collected from records of neonates diagnosed for neonatal meningitis infection cases for the last ten years (Jan, 2001 to Dec, 2010).

3.3. Source Population

The source population for the study was all neonates who had been admitted at Tikur Anbessa Specialized Hospital within the specified period (January, 2001 to December 2010).

3.4. Study population

During the study, all neonates who had attended in the neonatal care unit at Tikur Anbessa Specialized Hospital for bacterial meningitis cases within the specified period (January.2001 to December 2010) were included as sample of the study.

3.5. Eligibility and Exclusion Criteria

3.5.1. Inclusion Criteria

All neonate patients listed in bacteriology culture registration book for CSF and blood examination for neonatal bacterial meningitis infection cases and had complete documents at Tikur Anbessa Specialized Hospital during the specified period (January, 2001 to December 2010) were included in the study.

3.5.2. Exclusion Criteria

CSF and blood samples submitted without appropriate data and incomplete documentation were excluded from the study.

3.6. Study Variables

The characteristics (variables) such as, sex, age of newborn, year, birth weight, gestational age, isolated organism, and treatments were assessed in the study

3.6.1. Dependent Variables

Isolated pathogens (etiologic agents for neonatal bacterial meningitis infection)

3.6.2. Independent Variables

Sex, age, birth weight, gestational age, and year were included in the study.

3.7. Sample size

A total of 2510 neonate patients suspected with bacterial meningitis at Tikur Anbessa specialized Hospital between January 1, 2001 to December, 31, 2010 were included in the study.

3.8. Data Collection and Processing

3.8.1. Sample Collection

All relevant data was taken from bacteriology culture registration book for CSF and blood examination for neonatal meningitis infection cases and kept in Tikur Anbessa Specialized Hospital using data collection form.

3.8.2. Procedures

In this study certain procedures relevant to the case were implemented. These procedures include

- ❖ Direct contact with concerned personnel in the Hospital
- ❖ Then after all clinical data relevant for the study was taken from bacteriology culture registration book that were recorded in the last ten years and kept in Tikur Anbessa Specialized Hospital using data collection form.

- After data collection, the data were entered into computer
- Finally, the data were analyzed using appropriate statistical methods (initially using manual tabulation, graphs, and tables later using SPSS17.0).

3.8.3. Quality Control

Reliability and representativeness of a study is partly measured by its quality control approaches in each steps of carrier. Thereby in this study, certain quality control measures were taken to assure quality of the study. These measurement strategies include:

- Exclusion of incomplete data in a specific year of study
- Inclusion of complete and specific data only in respective years of study
- To keep quality of the data, data were entered into the SPSS twice

3.8.4. Data Entry and Analysis

Data entry and analysis was done using SPSS Version computer 17. Prevalence rate was calculated for the sum of numbers of etiologic agents examined within each respective year.

3.9. Ethical Consideration

This M.Sc research project work was approved by Department ethical and review committee (DERC) of Microbiology, Immunology and Parasitology (DMIP), Addis Ababa University and permission were obtained from Tikur Anbessa Specialized Hospital Administrator. Moreover all essential ethical considerations to insure the confidentiality of the identity of patients (neonatal care unit attendants) were taken. The patients‟ cards had been used only for the purpose of this research project. However, due to the nature of this study (A retrospective study), informed consent had not needed. A letter informing the medical director of the Hospital about the objective of the study was written from the university, from Dep‟t of microbiology prior to actual data collection period.

4. RESULTS

4.1. Demographic Descriptions of the Study Subjects

During the 10-year time period considering for this retrospective study two thousand five hundred and ten neonate patients with suspected bacterial meningitis were examined using blood and CSF culture in bacteriology laboratory at Tikur Anbessa Specialized Hospital. One thousand three hundred and twenty one (52.6%) were male, while one thousand one hundred and eighty nine (47.4%) were female; Making male to female ratio 1.1:1. One thousand three hundred and seventy (54.6%) neonate patients have less than or equal seven days age, while one thousand one hundred and forty (45.4%) have greater than seven days of age. 53(57.61%) were having preterm birth(<37 weeks gestational age),while 39(42.39%)had full term gestational age(>36 weeks gestation),and 54(58.70%) were having <2500gm birth weight and (LBW), 32(34.78%) had 2500-4000gm and (normal birth weight), while 6(6.52%) had >4000gm birth weight and (high birth weight)(Table 1)

Table 1: Age, sex, gestational age, and birth weight of patients diagnosed with neonatal bacterial meningitis at TASH, from January 1, 2001 to December 31, 2010

Characteristics of variables		Frequency	Percent (%)
Gender	Male	1321	52.6
	Female	1189	47.4
	Total	2510	100.0
Age	<=7days	1370	54.6
	>7 days	1140	45.4
	Total	2510	100.0
Gestational age of neonates	Preterm	53	57.61
	Term	39	42.39
	Total	92	100.00
Birth weight of neonates	<2500gm	54	58.70
	2500-4000gm	32	34.78
	>4000gm	6	6.52
	Total	92	100.00

4.2. Specimen Collected and Bacteria Isolated

Out of the total 2510 clinical specimen from suspects of neonatal bacterial meningitis, 1189(47.4%) were CSF and 1321 (52.6%) were blood. From1189 CSF and 1321 blood specimen pathogenic bacteria isolated were 56 and 358 respectively. The isolation rate from CSF and blood were 4.71% and 27.1% respectively. The overall isolated bacteria 414 and isolation rate was 16.49 %(Table 2)

Table 2: Bacterial pathogens isolated from blood and CSF cultures for neonatal bacterial meningitis suspected cases at TASH, from January 1, 2001 to December 31, 2010

Isolated pathogens	Types of specimen		Total
	Blood	CSF	
No bacterial growth	963	1133	2096
Klebsiella Spp.	45	5	50
S.pneumoniae	2	13	15
S.pyogens	5	3	8
S.aureus	62	3	65
E.coli	19	9	28
Acinetobacter	38	7	45
N.meningitidis	1	5	6
H.influenzae	1	1	2
Coag-negative-staphylococcus	146	2	148
Non-group-A-streptococcus	4	2	6
Salmonella	13	2	15
Entrobacter	5	0	5
Others	17	4	21
Total	1321	1189	2510
Total -positive cases	**358**(27.10%)	**56**(4.71%)	**414**(16.49%)

4.3. Bacterial Etiologies

A total of 2510 bacterial culture was done in the bacteriology laboratory and the most common isolated pathogens and their isolation rate out of the total suspected meningitis cases were *Coagulase-negative-staphlococcus* 148(5.9%), *S.aureus* 65(2.6%), *K.pneumoniae* 50(2.0%), *Acinetobacter* 45(1.8%), *E.coli* 28(1.1%), *S. pneumoniae* 15(0.6%), *Salmonella* 15(0.6%), *S.pyogens* 8(0.3%),*N.meningitis* 6(0.2%), *Non-group-A-streptococcus* 6(0.2%), *Entrobacter* 5(0.2%), *H.influenzae* 2(0.1%) and there were no bacterial growth from1133(45.1%) and 963(38.4%) CSF and blood culture respectively.

The overall isolated bacterial etiologies were 414 showing an isolation rate of 16.49%. No mixed bacterial infection was observed and the most common isolated pathogens were *Coagulase-negative-staphylococcus* 148(35.75%), *S.aureus* 65(15.70%), *K.pneumoniae* 50(12.08%), *Acinetobacter* 45(10.87%), *E.coli* 28 (6.76%), *S. pneumoniae* 15(3.62%), *Salmonella* 15 (3.62%), *S.pyogens* 8(1.93), *N.meningitis* 6(1.45%), *Non-group-A-streptococcus* 6(1.45%), *Entrobacter* 5(1.21%), *H.influenzae* 2(0.48%) and 21(5.07 %) cases of meningitis were due to other bacterial etiology(figure 1).

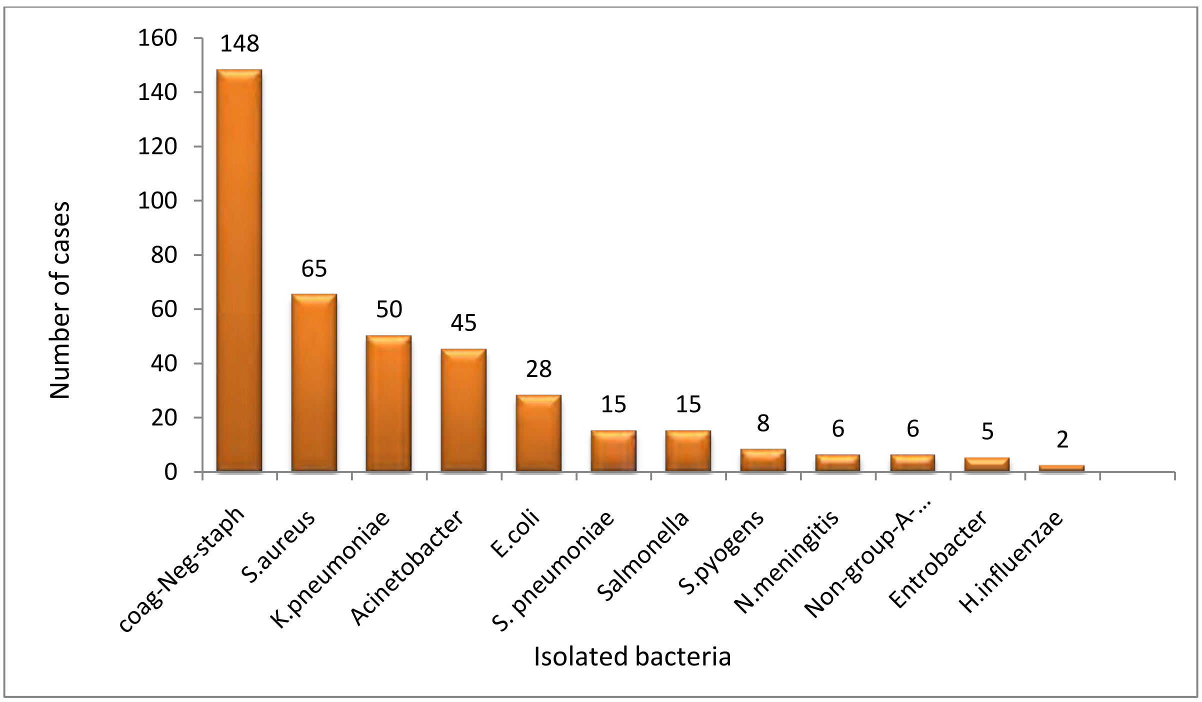

Figure 1: Relative incidence of bacterial species isolated from CSF and Blood culture of neonate patients suspected for meningitis at TASH, from Jan 1, 2001 to Dec, 2010.

4.4. Trends of Bacterial Meningitis Cases of Neonate Patients

The numbers of neonatal bacterial meningitis cases in each year from January 1, 2001 to December 31, 2010 were 41, 18, 16, 50, 54, 46, 44, 45, 40 and 56, respectively and the positive isolation rates in the same year were 13.6%, 14.6%, 17.0%, 25.1%, 20.8%, 26.1%, 15.5%, 15.5%, 12.8% and 12.6% respectively.56 (13.5%) of bacterial pathogen were isolated only in the year 2010. Higher peak had been observed from the year 2004 to 2006. This may be due to higher number of admitted patients and had been properly documented in their medical record profile or probably in these respective years there was high incidence of bacterial meningitis (Table 3)

Table 3**:** Trends of bacterial meningitis cases isolated from CSF and blood culture of neonate patients at TASH, from January 1, 2001 to December 31, 2010.

Isolated bacterial	Year										
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	Total
No bacteria growth	260	105	78	149	206	130	239	268	273	388	2096
Klebsiella Spp	3	3	2	4	7	8	2	11	3	7	50
S.pneumaniae	3	0	0	2	2	2	1	4	0	1	15
S.pyogens	4	0	1	1	1	0	0	1	0	0	8
S.aureus	2	4	4	2	8	6	13	7	6	13	65
E.coli	2	0	2	3	2	6	3	5	2	3	28
Acinetobacter	1	2	1	5	7	4	2	6	9	8	45
N.meningitidis	4	0	0	0	0	0	0	0	2	0	6
H.influenzae	1	0	0	0	0	0	0	0	0	1	2
Coag-Negative-staph	14	8	3	26	27	14	16	11	13	16	148
Non-Group-A- strept	0	0	0	2	0	0	2	0	1	1	6
Salmonella	0	0	1	3	0	4	2	3	1	1	15
Entrobacter	1	0	0	0	0	0	0	0	2	2	5
Others	6	1	2	2	0	2	3	1	1	3	21
Total	301	123	94	199	260	176	283	317	313	444	2510
Total-Positive	41	18	16	50	54	46	44	49	40	56	**414**
Prevalence	13.6%	14.6%	17.0%	25.1%	20.8%	26.1%	15.5%	15.5%	12.8%	12.6%	**16.49%**

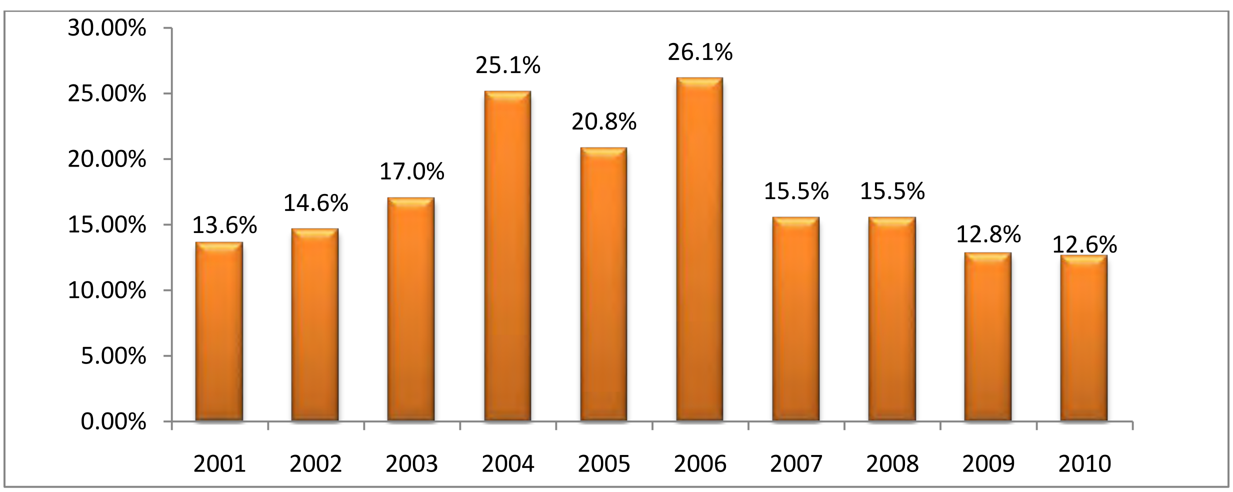

Figure 2: Trends of neonatal bacterial meningitis cases isolated from CSF and blood culture of neonate patients at TASH, from Jan 1, 2001 to Dec. 31, 201

From the total of 414 positive neonatal bacterial meningitis cases 208(15.18%) were having <=7days age, while 206 (18.07%) were having >7 days of age. The common causative organisms were slightly evenly distributed between early-and late-onset meningitis infection. There was no stastical significance association with isolated bacteria pathogens and neonates‟ age (Chi-Square=16.27, P value =0.235) (Table 4)

Table 4:-Neonatal age and isolated pathogen distribution of neonate patients positive for bacterial meningitis cases at TASH, from Jan 1, 2001 to Dec. 31, 2010

Isolated pathogens	Neonates age		Total
	<=7days	>7days	
No bacteria growth	1162	934	2096
Klebsiella Spp	25	25	50
S.pneumoniae	6	9	15
S.pyogens	4	4	8
S.aureus	38	27	65
E.coli	16	12	28
Acinetobacter	23	22	45
N.meningitidis	1	5	6
H.influenzae	1	1	2
Coag-negative-staphylococcus	70	78	148
Non-group-A-strepptococcus	3	3	6
Salmonella	4	11	15
Entrobacter	4	1	5
Others	13	8	21
Total	1370	1140	2510
Total –positive cases	**208** (15.18%)	**206** (18.07%)	**414** (16.49%)

4.5. Risk Factors Associated with Neonatal Meningitis Infections

Out of the total 414 positive for neonatal bacterial meningitis cases only 92 had full documented medical record profile to assess some associated risk factors for neonatal bacterial meningitis infection; Birth weight and gestational age of neonates. Fortunately there were no known maternal risk factors. Of 92 positive cases 53(57.60%) were having preterm birth (<37weeks gestation) and low birth weight (<2500g), while 39(42.40%) were having full term birth (>37weeks gestation) and had normal birth weight (2500-400g) and high birth weight (>4000g). There was stastical significance association within gestational age of the neonates and their birth weight (Chi-Square=4.91, P value =0.000). More than 50% of the cases have preterm maturation and low birth weight. This reveals that preterm maturation was the risks for low birth weight and on the other hand it was the risks for neonatal meningitis infection and other bacterial infections for the new born babies (figure 3).

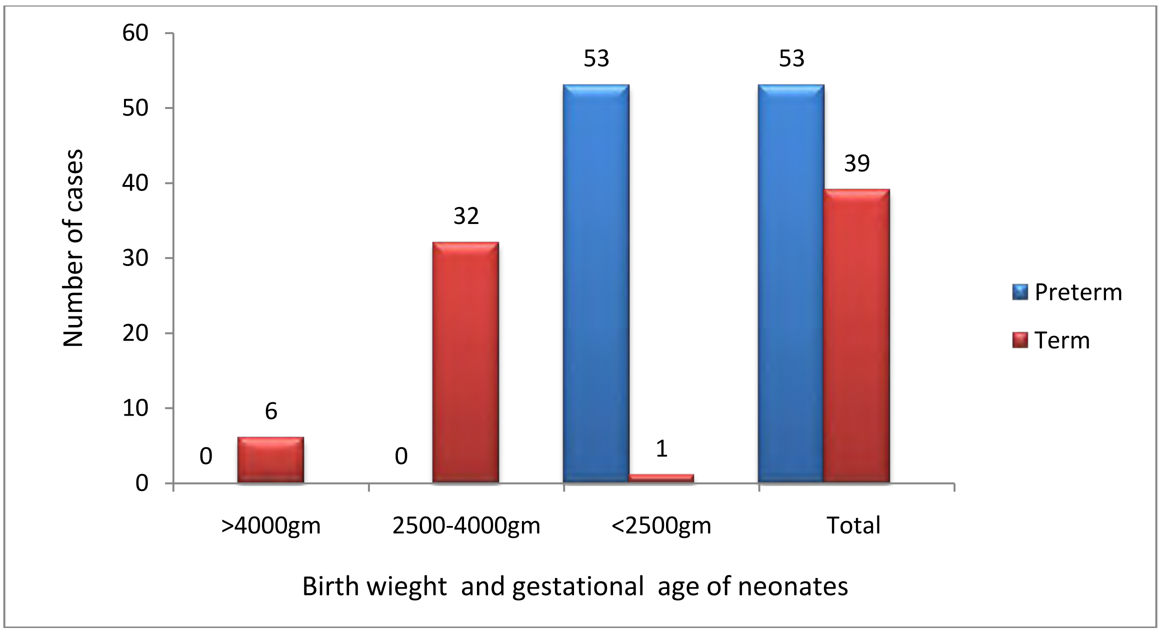

Figure 3: Birth weight and gestational age distribution of 92 neonate patients positive for bacterial meningitis cases at TASH, from Jan 1, 2001 to Dec. 31, 2010

4.5.1. Gestational age, Birth Weight and Isolated Pathogen

From 92 positive meningitis cases having gestational age and birth weight documented medical profile from patients‟ cards 57.61% of causative agents for neonatal bacterial meningitis infection had been isolated from neonates having preterm birth than full term. The most common isolated pathogen from neonates having <37 weeks gestational age were *Klebsiella Spp, S.aureus, E.coli, Acinetobacter, Non-group-A-streptococcus* and *salmonella*, while *Coagulase-negative-staphylococcus* and *N.meningitidis* were isolated from full term neonates. There was stastical significance association within isolated pathogens and their gestational age (Chi-Square=5.78, P value=0.000). This indicated that preterm birth of neonates (<37weeks gestation) have greater risks for neonatal meningitis infection and other bacterial infections than those neonates having full term gestational age (>36weeks gestation) (Table 5)

Out of 92 positive cases, 58.70% of the etiologic agents for neonatal meningitis infection cases were also isolated from neonates having low birth weight (<2500gm) than normal (2500-4000gm) and high birth weight (>4000gm). There was stastical significance association with neonates‟ birth weight and isolated bacteria pathogens causative for neonatal meningitis infections (Chi-Square=6.41, P value =0.000). This shows that low birth weight and preterm birth of neonates have greater risks for neonatal bacterial meningitis infection and other bacterial infections than those neonates having normal birth weight and full term gestational age, since more than 50% of positive cases had preterm birth and low birth weight (Table 5)

Table 5: Gestational age, Birth weight and isolated bacterial pathogens distribution of 92 neonate patients positive for bacterial meningitis at TASH, from Jan 1, 2001 to Dec. 31, 2010

Isolated pathogen	Gestational age of neonates		Total	Neonates‟ Birth weight			Total
	Preterm	Term		>4000g	2500-4000g	<2500g	
Klebsiella Spp	7	4	11	1	3	7	11
S.pneumoniae	2	2	4	0	2	2	4
S.pyogens	1	0	1	0	0	1	1
S.aureus	10	8	18	1	7	10	18
E.coli	5	1	6	1	0	5	6
Acinetobacter	5	4	9	1	3	5	9
N.meningitidis	1	2	3	1	1	1	3
H.influenzae	1	0	1	0	0	1	1
Coag-negative-staph	15	16	31	1	14	16	31
Non-group-A-strept	2	0	2	0	0	2	2
Salmonella	2	1	3	0	1	2	3
Entrobacter	0	0	0	0	0	0	0
Others	2	1	3	0	1	2	3
Total	**53** (57.61%)	39(43.39%)	92 (100%)	6 (6.52%)	32 (34.78%)	**54** (58.70%)	92(100%)

4.6. Antibiotic Prescribed

From 92 neonate patients positive for bacterial meningitis cases having full documented medical profile for further assessing of associated risk factors for neonatal meningitis infection; birth weight and gestational age only 75 cases have been given single and multiple drugs for treatment. 66 (88%) of the cases had given multiple drugs, Ampicillin with gentamycin, 3(4%) have been given vancomycin, 2(2.67%) were given gentamycin, while 4(5.33%) had given other treatment. More cases were treated with the combination of ampicillin and gentamycin (Table 6).

Table 6: The treatment given for 75 neonate patients positive for bacterial meningitis cases at TASH, from January 1, 2001 to December 31, 2010

Treatment(drugs)	Frequency	Percent (%)
Ampicillin with Gentamycin	66	88
Vancomycin	3	4
Gentamycin	2	2.67
Other drugs	4	5.33
Total	75	100%

5. DISCUSSION

Neonatal meningitis is an illness characterized as a result of infection and inflammation of the meninges and it typically happens between birth and the first 28 days of life. The bacterial meningitis infection is more common during the first month after birth compared to other stages of newborns and it is associated with high morbidity and mortality (Luzia *et al*., 2007).

In this study, the overall prevalence of bacterial meningitis infection among neonates in the last ten years at Tikur Anbessa Specialized hospital was (16.5%) which was higher than the previous hospital population-based retrospective study of neonatal bacterial meningitis conducted in Addis Ababa, which was with an overall prevalence of 9% (Gebremariam,1998). This slight increase and difference in the prevalence of neonatal bacterial meningitis infection in our study and the previous one may be due to samples and sampling techniques, since in the present study the sample were both blood and CSF culture from meningitis suspected cases, while the previous study was only from CSF culture:

But the data derived from our studies agree with the findings reported in Kenya which was 17.9 %(Laving *et al.,* 2003). However, low prevalence of neonatal bacterial meningitis was observed in Thailand 12.5 %(Chotpitayasunondh, 1994), in Australia 9.2 %(May *et al*., 2005), Wichita, USA 8.4 %(Michael *et al.,* 1985). This may be due to the increasing of community health management and improved antenatal care as well as increasing of health education to the community to reduce the likelihood of neonatal bacterial meningitis infection as well as other infections in developed countries.

In this retrospective study the major organisms responsible for neonatal bacterial meningitis were C*oagulase-negative staphylococcus* (35.75%), *S.aureus* (15.70%), *K.pneumoniae* (12.08%), *Acinetobacter Spp* (10.87%), *E.coli* (6.76%) and *S.pneumoniae* (3.62%). *Coagulase- negative-staphylococcus* remains the leading etiological agent for neonatal bacterial meningitis infection over the study period; Accounting for 148(35.5%) of the total case in our study. A similar result reported from Cleveland, Ohio 43% (Benedict *et al*., 2010), United States 22 %(Alistair and Philip, 2003) *Coagulase-negative-staphylococcus* was the most common causative agent for neonatal bacterial meningitis infection and sepsis.

Since, in very low birth weight neonates (<1.5kg) and preterm birth *Coagulase-negative staphylococci* need to be considered strongly as causative organisms in neonatal bacterial meningitis and sepsis, and

VLBW infants are at particularly high risk, in large measure because of less efficient defense mechanisms and deficient transfer of antibodies from mother to baby (which occurs predominantly after 32 weeks" gestation) (Benedict *et al*., 2010, Alistair and Philip, 2003)

However, K.pneumaniae were found to be the most common causative agents for bacterial meningitis among neonates as reported from Ethiopia, Addis Ababa 22%(Gebremariam, 1998), in Jordan 40%(Daoud, 1996), in Iran 35.5%(Aletayeb, 2010). Other study in Australia (Francis and Gilbert, 1992), in Trinidad, western India (Ali.1995), in London (Heath, 2003, Louvios *et al.,* 1991) and Canada (Stevens *et al.,* 2002) reported that Group B *streptococcus* and *E.coli* to be the major cause of neonatal meningitis infection. In developing countries, Group B streptococcus appears to be much less frequent, although this is not universal (Heath, 2003). The microorganisms causing neonatal meningitis not only vary between different countries, but show temporal changes within the same country (Klein, 2000).

Staphylococcus aureus was found to be the second cause of neonatal bacterial meningitis in the present study next to *Coagulase-negative streptococcus*. Sixty five (15.70%) cases of *S. aureus were* detected in the last ten years. This finding was in line with the research conducted from West Africa, Nigeria 13% (Airede *et al.,* 2008).

In this study the major organisms responsible for neonatal bacterial meningitis were slightly evenly distributed between early and late-onset meningitis, and among term and preterm newborns. But a study conducted in India (Ali 1995), London (Louvois, 1991), Oxford (Hristeva, 1993) reported that Group B *streptococcus* was common in early onset meningitis infections. But in our finding group B *streptococcus* was not found.

In our study of 2510 clinical specimens from suspects of neonatal bacterial meningitis 1189(47.4%) were CSF and 1321(52.6%) were blood. From 1189 CSF and 1321 blood specimens pathogenic bacteria isolated were 56 and 358 respectively and the isolated rate from CSF and blood culture were 4.7% and 27.1% respectively. In the present finding more etiologic agents were isolated from blood than CSF culture. Similar finding was reported from United States (Harmony *et al.,* 2006). But, In contrast to our finding other studies from Kenya (Laving *et al.,* 2003), Nigeria (Airede,*et al.,*2008), Jordan (Daoud *et al.,* 1996), Oxford (Hristeva *et al.,* 1993) reported that more etiological agents for meningitis infection were isolated from CSF than blood culture. This difference may be due to sampling technique, laboratory procedures, and technical appropriateness during blood and CSF culture and culture media they were using. Other studies conducted in Addis Ababa (Gebremariam, 1998), Gondar (Andargachew, 2005), India (Ali, 1995, John *et al.,* 1976) use only the confirmatory test (CSF) for meningitis infection diagnosis to be clear that the neonates have meningitis infection.

In our result 58.70% of positive case for neonatal bacterial meningitis infection had low birth weight and 57.61% were having preterm maturation infections and the isolated pathogens were having higher prevalence in preterm and in low birth weight neonates than those having full term gestation and normal birth weight, and there was significance association ($p<0.05$). A similar finding reported from Nigeria (Airede *et al.,* 2008), Australia (Francis and Gilbert, 1992), in Trinidad, west India (Ali, 1995), Brazil (Luzia *et al.,* 2007) and Jordan (Doaud *et al.,* 1996), Oxford (Hristeva *et al.,* 1993) stated that low birth weight showed higher risk of neonatal bacterial meningitis and was significantly more likely in the preterm($p<0.05$). Hence, low birth weight and preterm maturation (<37weeks gestation) were greater risks factors for neonatal bacterial meningitis infections. There is evidence to suggest that meningitis in preterm low birth weight and sickly babies is caused by organisms, usually from the maternal genital tracts, which do not have recognized pathogenecity factors. However, late onset infection is associated with organisms with recognized virulence and pathogenicity factors, many of which have a predisposition to the central nervous system (Louvois, 1994).

In our study out of 75 positive neonatal bacterial meningitis cases that have been properly treated with single and multiple drugs, 66(88%) were given a combination of ampicillin with gentamycin, 3(4%) had given vancomycin, 2(2.67%) treated with gentamycin, while 4(5.33%) were given other treatments, and more meningitis cases have been treated with the combination of ampicillin and gentamycin. Similar study were reported from Nigeria (Airede, 1993), Egypt (Speer, 1986) and Jordan (Daoud *et al*., 1996). Since, Ampicillin and/or gentamycin were effective in vitro against all microorganisms which caused septicemia or meningitis within the first four days of life (Airede. 1993, Speer. 1986). Another finding reported from most centers in the United States, a combination of ampicillin with an aminoglycoside (usually gentamycin) is generally effective in the first week after birth (Alistair and Philip, 2003). However, Heath (2003) reported that Empirical therapy for meningitis in the first week of life: ampicillin + gentamycin + cefotaxime and Empirical therapy for meningitis after the first week of life: ampicillin + cefotaxime + an amino glycoside. In contrast to the above reports the study conducted in Kenaya (Laving, 2003) Most blood and CSF isolates were resistant to ampicillin and gentamicin but showed good *in-vitro* sensitivities to amikacin, ceturoxime and the third generation cephalosporins (ceftriaxone, ceftazidime and cefotaxime).

6. Limitation of the Study

The following was the limitation of the present study

- ❖ Incompleteness (missing) of some figures (test results) in the bacteriology laboratory register books as well as in patients‟ medical record profile may have its own disadvantage in the study result and analysis, and reduced the comprehensiveness of this project.

- ❖ Some relevant variables such as known maternal risk factors, route of delivery, maternal age, educational status, some socioeconomic status of parents and outcomes of treated neonate patients, were not included in neonate patients‟ medical records profile. These variables would have been essential to assess the possible associated risk factors for neonatal meningitis infection.

- ❖ This was hospital population-based data, and cannot represent the general population

7. Conclusion

- In our study the overall prevalence of bacterial meningitis among neonates who had admitted at TASH was higher than the previous study conducted in the same study area.

- *Coagulase negative staphylococcus* constituted 148(35.75%) and it is the lead cause of neonatal bacterial meningitis infection during the ten years of study period and slightly evenly distributed in early and late-onset meningitis infections. *S.aureus* was the second common cause of neonatal bacterial meningitis infection followed by *K.pneumoniae* in our study.

- Higher number of etiological agents for neonatal bacterial meningitis infection have been isolated from neonates having preterm birth (<37 weeks gestation) and low birth weight.

- In our result more than 50% of positive cases for neonatal bacterial meningitis were having low birth weight and preterm birth.

- In the present study of the total neonate patients‟ positive for bacterial meningitis more patients were treated with a combination of ampicillin and gentamycin.

8. Recommendations

On the bases of these retrospective study findings it is recommended that:

- Efficient meningitis surveillance, including laboratory data, is necessary to monitor the disease trend, population at risk, serotype distribution.
- Educate women (particularly pregnant women) about the risks of getting preterm birth and low birth weight baby, and to reduce neonatal bacterial meningitis infections as well as other bacterial infections during pregnancy and during giving delivery.
- The hospital should have safe and sound, well organized delivery room, proper obstetric management and antenatal care to reduce neonatal bacterial meningitis infection as well as other infections.
- Data recorded system in the laboratory as well as in other medical record profile should be upgraded. All the laboratory staffs that carry out the laboratory work should be trained to record all the available patients‟ data in the register book, since it is necessary for further research project works.

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Appendix I

Data collection form

No_	Date of admission	Lab. No	Case No	Sex of NBB	Age of NBB	Gestational age	Weight at birth	Lab. Diagnosis (CSF, Blood)	Isolated organism (Lab. finding)	Treatment(Drugs)

NB:-Lab=laboratory, NBB=new born baby, Kg=kilo gram, CSF= Cerebrospinal fluid

Appendix-II

Declaration

Title: A retrospective study on the prevalence, etiological agents and associated risk factors for neonatal bacterial meningitis infection, Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

I, the under signed, declare that this M.Sc research project is my original work, has not been presented for any degree in Addis Ababa or any other university. I also declare that all sources of materials used for the research project have been properly acknowledged.

Name of candidate: Melese Abate

Signature...

Place...

Date of submission.....................................

This research project has been submitted for examination with my approval or university advisor

Name of advisor: Mr. Tamrat Abebe

Signature...

Place...

Date of submission.....................................

Name of examiner: Prof. D.P. Monga

Signature..

Place..

Date of submission....................................