College of Health Sciences, School of Pharmacy

Department of Pharmacology and Clinical Pharmacy

Treatment Outcome of Neonatal Sepsis and Associated Factors among Neonates Admitted to Neonatal Intensive Care Unit of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia: A Retrospective Cohort Study.

By: Bethlehem Lemma (BPharm)

February, 2022

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A Thesis to be Submitted to the Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University in Partial Fulfillment for the Requirements of Master of Science Degree in Pharmacy Practice.

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Addis Ababa, Ethiopia

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This is to certify that the thesis prepared by Bethlehem Lemma, entitled with: **Treatment Outcomes of Neonatal Sepsis and Associated Factors among Neonates Admitted to Neonatal Intensive Care Unit of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia: A Retrospective Cohort Study.** Submitted in partial fulfillment of the requirements for the degree of Master of Science in Pharmacy Practice complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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January, 2022

Addis Ababa, Ethiopia

Abstract

Treatment Outcome of Neonatal Sepsis and Associated Factors among Neonates Admitted to Neonatal Intensive Care Unit of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia: A Retrospective Cohort Study.

Bethlehem Lemma (BPharm), Addis Ababa, 2021

Globally, neonatal sepsis is a major cause of neonatal death. A definitive early diagnosis and appropriate antimicrobial therapy which significantly reduce mortality are challenging in resource limited settings like Ethiopia. This study aimed to assess the treatment outcome and factors associated with neonatal sepsis mortality among those treated at the neonatal intensive care unit of Tikur Anbessa referral hospital (TASH), Addis Ababa, Ethiopia. A retrospective cohort study was conducted from September, 2018 to September, 2020.Neonates diagnosed with sepsis by the attending physician either clinically or laboratory-confirmation was included in the study. Data such as patient's age, sex, and address, type of antimicrobial administered, date of treatment started and completed, microbiological results and other clinical characteristics were collected retrospectively from medical chart. Data were entered and analyzed using the Statistical Package for Social Sciences version 25. Survival analysis was performed using Kaplan Meier Method. Log-rank test was used to determine survival period differences and cox hazard regression was used to identify associated factors of neonatal mortality. Systematic random sampling technique was employed to recruit the study participants. Binary logistic regression was used to predict determinants of length of hospital stay. Statistical significance was declared at p-value <0.05.The total number of neonates in this study was 206. One hundred ninety three (93.7%) neonates have survived from neonatal sepsis and 77 (37.4%) of the neonates stayed in the hospital for more than seven days. Multivariable analysis showed that risk hazard of neonatal mortality was 5.486 higher among pregnant women with history of vaginal discharge compared to pregnant women's without discharge (AHR, 5.486, 95% CI: 1.308-26.134).Conversely, absence of Premature rupture of membranes (PROM) (0.503 CI: 0.326-0.776) and those neonates delivered through SVD (AHR 0.265, CI: 0.091-0.767), were associated with decreased risk of mortality.

Kaplan-Meier survival analysis using log-rank test shows there was a statistically significant decrease in survival period among neonates delivered through spontaneous vaginal delivery (SVD) than neonates delivered by caesarian section (CS) (p = 0.014).

Low-birth weight (AOR=11.87, 95%CI: 2.344-60.15) and being on Ampicillin (AOR=16.09, CI: 4.484-57.74) were associated with prolonged hospitalization.

On the other hand, being female (AOR= 0.090, 95%CI: 0.018-0.458); absence of GI symptoms (AOR= 0.214, 95%CI: 0.19-0.350); and antibiotics dose change from initial treatment (AOR= 0.081, 95% CI: 0.001-0.703) were associated with a decreased rate of hospitalization. The Obstetrics and gynecology department should promote delivery though SVD, and to increase Antenatal care and aggressively manage of pregnant women with vaginal discharge as it significantly affects the outcome of their newborns with neonatal sepsis. Emphasis should be given on meticulous management of neonatal sepsis and early change of antibiotics is imperative when needed as it reduces length of hospital stay thereby decreasing mortality.

Keywords: Hospitalization, Neonates, Neonatal Sepsis, Ethiopia, Treatment Outcome,

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First of all, I would like to thank the almighty GOD who helps me in my entire life. Next to this, I would like to express my gratitude to Addis Ababa University College of Health Sciences, School of Pharmacy and Black Lion Hospital for giving this opportunity to study on one of the major causes of neonatal mortality. Also want to say thank you to my advisors EskinderAyalew (BPharm, MPharm, Assistant professor), Dr, Workeabeba Abebe (MD, MPH V/ Chair, Department of Pediatrics and Child Health Associate Professor of Pediatrics). Finally my gratitude goes to Atalay Mulu (BPharm, MPharm) and Abdella Birhan (BPharm, MPharm) for their continuous support.

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List of Abbreviations

AAU	Addis Ababa University
ANC	Antenatal care
CONS	Coagulase Negative Streptococcus
CS	Caesarian Section
EDHS	Ethiopian demographic and health survey
EONS	Early-onset neonatal sepsis
GBS	Group B Streptococcus
LBW	Low birth weight
LONS	Late-onset neonatal sepsis
NICU	Neonatal intensive care unit
NS	Neonatal sepsis
PROM	Premature rupture of membranes
STI	Sexually transmitted infection
SVD	Spontaneous Vaginal Delivery
TASH	Tikur Anbessa specialized Hospital
UTI	Urinary tract infection

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1. Introduction

1.1. Background

Neonatal sepsis (NS) is an infection involving bloodstream in infants≤28 days. It can be manifested as pyelonephritis, gastroenteritis, meningitis, pneumonia, or the presence of fever(Aggarwal*et al.*, 2001; Hanumantha and Tabaseera, 2017).The global epidemiological burden of sepsis is difficult to ascertain. Because outcomes of neonatal sepsis treatment at different settings vary due to Pathogens and sensitivity patterns are changing every time(Bunduki, G.K., Adu-Sarkodie et.al 2019),Introduction of broad-spectrum antibiotics (Amy L Pakyz et al February 2021) and Affordability of medications, availability of alternatives in resource-constrained settings like in Ethiopia (Tadesse et al,2021) There are an estimated 1.3 to 3.9 million annual neonatal sepsis cases and 400,000 to 700,000 annual deaths worldwide(WHO, 2020).

Neonatal sepsis is categorized as early-onset neonatal sepsis EONS) which occur in the first week (0-7 days of age), mainly due to bacteria acquired before and during delivery in which Infection can occur via hematogenous, trans-placental spread from an infected mother . The other category is late-onset neonatal sepsis (LONS) which usually present between 7-28 days of age and acquired after delivery(Vergnano*et al.*, 2005; Tewabe *et al.*, 2017).Early onset neonatal sepsis is 2.6-fold more common than LONS(Afrin1 *et al.*, 2016)

The major risk factors for EONS are preterm birth, maternal colonization with *Group B Streptococcus*(GBS), foul-smelling, rupture of membranes >18 hours, and maternal signs or symptoms of intra-amniotic infection. Other variables include low socioeconomic status, male sex, and low Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) scores (Aggarwal*et al.*, 2001; Polin, 2015).On the other hand; having prematurity, mechanical ventilation, admission in intensive care unit, low birth weight , and invasive procedures increases risk the of LONS(Khan *et al.*, 2012; Hanumantha and Tabaseera, 2017).

Neonates with sepsis may present with one or more of the following sign and symptoms. Hypothermia or fever (hypothermia is more common in preterm low birth weight infants), lethargy, poor cry, refusal to suck, poor perfusion, prolonged capillary refill time, absent neonatal reflexes, brady/tachycardia, respiratory distress, apnea and gasping respiration, hypo/hyperglycemia and metabolic acidosis(Aggarwal*et al.*, 2001; Vergnano *et al.*, 2005).

The clinical diagnosis of sepsis in the neonate is difficult because many of the signs of sepsis are nonspecific and are observed with other noninfectious conditions. Available diagnostic testing does not help to decide which neonate requires empirical antimicrobial therapy but can assist with the decision to discontinue treatment(Vergnano*et al.*, 2005; Polin, 2015). Blood culture is a gold standard for the diagnosis of sepsis. Single blood culture in a sufficient volume is required for all neonates with suspected sepsis(Wale Alemnew, Chelkeba Legese, Wobie Yohannes, 2021)

The pathogens most often implicated in neonatal sepsis in developing countries differ from those seen in developed countries(FuchStatewidesa*et al.*, 2016).The commonest causes of neonatal bacteremia in resource limited country are: *S. aurous*, *E. coli* and *Klebsiella spp*(Shitaye, 2008).

Risk factors associated with increased morbidity include multiple births, mothers who did not attend antenatal care Visits, neonates born by cesarean section, not initiated breast feeding within 1 h of birth(Woday*et al.*, no date; Worku *et al.*, 2012; Orsido, Asseffa and Berheto, 2019; Dessu *et al.*, 2020) ,prematurity, low birth weight(Leal *et al.*, 2012) preterm delivery, sub-optimal birth weight ,early onset sepsis and length of hospital stay(Atif M, Zia R, Malik I, et al., 2021).

An estimated 84% of neonatal deaths due to infections could be prevented through measures such as early diagnosis and timely, appropriate clinical management(WHO, 2020). Integrated Management of Childhood Illness (IMCI) guideline recommends providing prophylactic intramuscular (IM) or intravenous (IV) ampicillin and gentamicin in neonates with documented risk factors for infection for at least 2 days and to reassess. Treatment should be continued only if there are signs of sepsis (or positive blood culture). The IMCI recommends hospitalization and IM or IV antibiotic therapy with a combination of gentamicin and benzyl penicillin or ampicillin for at least 7–10 days(FuchStatewidesa*et al.*, 2016; WHO, 2020).Second generation cephalosporin's and vancomycin can be used based on the physician decisions. Length of hospitalization is considered based on the status of patient and culture result.

However, inappropriate antibiotic use is associated to the development and spread of resistant pathogens in the NICUs, also associated with adverse outcomes such as increased risk of candida invasive disease(WHO, 2020). Prolonged antibiotic therapy increases the risk of late sepsis, prolonged hospital admission and even death due to the nature of the disease and other factors, in many resource-constrained settings like in Ethiopia the degree of problem will be more. Hence, assessing treatment outcomes and contributing factors for mortality of neonatal sepsis through

continued research can assist in planning interventions to overcome the barriers and improve patient treatment outcomes.

1.2. Statements of the Problem

Neonatal mortality is a worldwide problem. The outcome of neonates with infections is strongly related to their appropriate diagnosis and management which is major challenge especially in low and meddle income country (LMIC)(Dessu*et al.*, 2020).This is due to lack of administration of intrapartum antibiotics to reduce the risk of vertical transmission, e.g. of *GBS*, from colonized mothers during or just before birth: Maternal micronutrient supplementation; poor identification of women at risk and poor post-partum care, during the first hours after birth and throughout the first month of life(FuchStatewidesa*et al.*, 2016; WHO, 2020).

Studies implicates that multiple birth, mode of delivery, breast feeding within 1 h of birth, birth weight of neonates and delayed treatment are commonly associated with adverse outcomes(Woday*et al.*, no date; Gebremedhin, Berhe and Gebrekirstos, 2015; Tewabe *et al.*, 2017; Dessu *et al.*, 2020). Neonatal deaths due to infections are preventable with accurate and timely diagnosis and treatment of neonatal sepsis. Due to prolonged hospitalization the neonate might develop new infection; increased cost of treatments, selection of antibiotics could be challenge due to antimicrobial resistance (AMR) finally death might occur.

Since treatment outcomes of neonatal sepsis and associated factors with mortality of neonatal Sepsis are not recently studied in our setup, findings of this study will help to identify the outcomes and associated factors with mortality in neonates treated at neonatal intensive care unit of Tikur Anbessa Specialized Hospital (TASH). As well as this study also used as a good input for further studies in related topics within the institution.

1.3. Significance of the Study

Sepsis is a medical emergency where each hour matters. Besides the growing burden of neonatal sepsis in developing countries including Ethiopia, awareness of the treatment outcome and many associated factors for neonatal mortality will enable us providing evidence-based care for neonates. Rapid treatment with antibiotics is mandatory for a favorable outcome, since there is no study on this setup regarding treatment outcome with survival analysis such as in-hospital patient condition and length of hospital stays, its mandatory to do research.

In the hope that this research will contribute to evidence based care for neonates, Described clinical presentations of neonatal sepsis at TASH, pattern of antibiotic use for treatments of neonatal sepsis at TASH, and also described the outcomes from these antibiotic treatment pattern and risk factors for outcomes.

Gives directions for policy makers and local governmental bodies to undertake preventive measures on the community, especially on pregnant mothers. Adds to the existing knowledge, Identified maternal risk factors of neonatal sepsis at TASH. Generates evidence that support existing knowledge of risk factors associated with neonatal sepsis mortality, identified risk factors for prolonged hospital stay .Generates better evidence on CS delivery and risk of neonatal sepsis mortality.

2. Literature Review

2.1. Introduction

The estimated global burden for neonatal sepsis was 2,202 per 100,000 live births(Aseffa and Abathun, 2020).The reported incidence of neonatal sepsis varies from3.59 to 8.910 per 1000 live births in South America and the Caribbean(Vergnano*et al.*, 2005)and from 7.113 to 3817 per 1000 live births in Asia, from 6.519 to 2315 per 1000 live births in Africa(Thaver and Zaidi, 2009).

Early onset neonatal sepsis mainly caused by ascending infection in the mother with chorioamnionitis, perinatal via direct contact in the birth canal and haematogenous spread. The main micro-organisms implicated causing include; *GBS*, *E- coli*, *Coagulase-negative Staphylococcus*, *H influenza* and *Listeria monocytogenes*(Dagnew *et al.*, 2013; Minyahil Alebachew Woldu*1, Molla Belay Guta2, Jimma Likisa Lenjisa2, Gobezie Temesgen Tegegne2, 2014) while LONS is usually acquired in the hospital after delivery having a catheter in a blood vessel for a long time, Staying in the hospital for an extended period of time(Freitas*et al.*, 2019; Bulbul, 2020).

Treatment objective is to alleviate the symptoms, avoiding life threatening complications and to have short hospital stay. Until culture report is collected the usual trend is to start broad-spectrum antibiotics with Ampicillin: 25 to 50 mg/kg/dose IV or IM, if Meningitis and severe *GBS* sepsis is suspected Ampicillin 100 mg/kg/dose plus Gentamicin: 4-5 mg/kg/dose IV and as an alternative third generation cephalosporin's such us Cefotaxime 50 mg/kg/dose IV or IM or with absences of hyperbilirubinemia ceftriaxone 50-100mg/kg can be used(Hospital and Health, 2011; Minyahil Alebachew Woldu*1, Molla Belay Guta2, Jimma Likisa Lenjisa2, Gobezie Temesgen Tegegne2, 2014; Tewabe *et al.*, 2017).

2.2. Treatment Outcome of NS

Late-onset sepsis and mortality among neonates in a Brazilian Intensive Care Unit: a cohort study and survival analysis were showed that 201 (13%) deaths, and of these, 54 (27%) occurred during antimicrobial treatment and without other apparent cause(Freitas*et al.*, 2019).while in Mexico, most infants with EOS survived to discharge,16% died;57% deaths were in the first 3 days of life. The case fatality rate was inversely related to Gestational Age (22–24weeks:54%; 25–28 weeks: 30%; 29–33 weeks: 12%; 34–36 weeks: 0%; 37 weeks: 3%).More infants with E Coli than with GBS infection died (33% vs 9%; P< .001). However, after adjustment for

Gestational Age, the risk of death was not significantly higher for infants with E Coli compared with GBS. Preterm infants with E Coli were more likely to have a fulminant illness with death in the first 3daysoflife(64%ofthosewho died)(J. *et al.*, 2017).while a study in Australia case fatality rate of 13.1% (95%CI 8.9-18.9%)(Al-taiar*et al.*, 2011).

A study conducted at Pakistan showed that the association of predisposing factors, clinical, and laboratory characteristics of the infected newborns with mortality by univariate methods and logistic regression analysis. Comparatively higher rates of mortality were seen among home-delivered newborn infants and those referred from other maternity facilities. The mortality was significantly higher among infants weighing < 1500 g and those with birth asphyxia P<0.05). The overall mortality was higher for gram-negative infections and the highest case fatality rates were seen in infections with Pseudomonas species (52%). Several clinical features suggestive of septicemia shock and metabolic derangement were associated with significantly increased risk of death. Of these, the logistic regression model identified hypotensive shock and acute renal failure as significant factors associated with the risk of death(Bhutta and Yusuf, 1997).

A study done in Nigeria reveals the finding of the comparisons between key characteristics of the Cases and those of the Controls using the Chi-squared analysis. It was found that the place of birth and the outcome were significantly associated with the development of sepsis with a case-fatality rate of 7.4% was observed(Ekwochi, Ifediora1 and Osuorah2, 2018). While a cross-sectional study in Congo showed the poor outcome among all the recruited neonates in 48 (21.1%) cases. Of the 69 neonates who had a positive blood culture, 20 (29.0%) had a poor outcome(Bunduki and Sarkodie, 2019). A study in Tanzania shows 46 (13.9%) neonates recruited in the study died,36 neonates out of 253(14.2%) was EOS while 10/77(13%) where LONS death(Bhutta and Yusuf, 1997).

A study in Qatar case-fatality rates of 17% and thirty septic neonates died during hospitalization. Neonates who developed fungal sepsis were nearly 10 times more likely to die during hospitalization than those who developed gram-positive or gram-negative sepsis. Septic, extremely low birth weight (<1,000g) neonates were found 3 times more likely to die during hospitalization compared to larger neonates. There was no significant increased risk of dying during hospitalization in septic males compared with females. On the other hand septic, neonates who had central venous lines (CVL) were almost 5 times more likely to die during hospitalization compared to those with no CVL however this was not statistically significant.

Septic term neonates were more likely to survive to discharge when compared with septic preterm neonates but this also was not statistically significant(Adugna Negussiea *et al.*, 2016).

Retrospective chart review was done in Felege Hiwot referral hospital, Bahirdar, Amhara Regional State, North West Ethiopia 2016 regarding the clinical outcome of neonatal sepsis: 189 (84%) were improved after treatment, 9 (4%) died and 13 (5.8%) referred to other organizations for further treatment. Respiratory distress syndrome and meconium aspiration syndrome were the determinant factors for poor outcomes of neonatal sepsis(Tewabe *et al.*, 2017).while in Jimma Prematurity (GA at birth,37weeks) was found to increase the likelihood of neonatal death as compared to term births. Premature and prolonged rupture of membrane before the onset of labor had increased the likelihood of neonatal death. Rupture of membrane 1– 12 hours before the onset of labor had a significantly higher risk of neonatal death as compared to the rupture of the membrane after the onset of labor(Debelew, Afework and Yalew, 2014).

A study was done in Southern Ethiopia a retrospective cohort study in 2019 there were 159 neonatal deaths during the follow-up time. Overall, the neonatal mortality incidence was 27 per 1000 neonates-days(Orsido, Asseffa and Berheto, 2019).A cohort of 3789 newborns that were admitted to the NICU of TASH shows there were 881 deaths in the study period making an early Neonatal mortality rate of 23.3% (233 per 1000 live births); 96.6% of the deaths occurred during the first three days of life and 60.7% of the infants were male. Firstborn, preterm, and low-birth-weight infants accounted for 20.5%, 52.5% and 59.3% of neonatal deaths, respectively, from each group. It was also higher in those whose mothers had no antenatal care follow up (34%), and who had a congenital anomaly (34.4%), prenatal asphyxia (PNA) (30.6%), respiratory distress (28.5%) and those who received oxygen treatment (31.6%)(Worku*et al.*, 2012). In the same setting but different study design, a 5-year retrospective case review was done which shows approximately 32% of deaths were documented as early death (within ≤24 h of arrival in the pediatric emergency department). More than half (59%) patients presented for treatment following at least two days of signs and/or symptoms and the highest mortality rate was seen in the neonatal age group (6%)(Jofiro*et al.*, 2018).

2.3. Organisms Causing Neonatal Sepsis

The pathogens most often implicated in neonatal sepsis in developing countries differ from those seen in developed countries(Vergnano*et al.*, 2005). Neonatal surveillance in developed countries generally identifies *GBS* and *E coli* as the dominant EONS pathogens(Vergnano*et al.*, 2005; Simonsen *et al.*, 2014; Tzialla *et al.*, 2015; J. *et al.*, 2017). which accounts for approximately

70% of infections combined(Simonsen*et al.*, 2014) and *CONS* the dominant LONS pathogen followed by *GBS* and *Staph. Aureus*(Vergnano *et al.*, 2005; Maramba-lazarte *et al.*, 2011; Khan *et al.*, 2012; Care *et al.*, 2013; Jyothi *et al.*, 2013; Simonsen *et al.*, 2014; Gebremedhin, Berhe and Gebrekirstos, 2015; Polin, 2015; Lamba *et al.*, 2016; Hanumantha and Tabaseera, 2017). However, inter-country variations are also apparent, with some South Asian reports suggesting a higher prevalence of *GBS* and some African reports the converse, or even no *GBS* isolates.

As the majority of studies in developing counties(mostly from Asia, Middle East and Africa) identified that *Klebsiella* (Maramba-lazarte *et al.*, 2011; Zakariya and Bhat, 2011; Khan *et al.*, 2012; Units *et al.*, 2012; Jyothi *et al.*, 2013; Afrin1 *et al.*, 2016; Lamba *et al.*, 2016;) and *Escherichia coli* (Maramba-lazarte *et al.*, 2011; Khan *et al.*, 2012; Dagnew *et al.*, 2013; Jyothi *et al.*, 2013; Lamba *et al.*, 2016) are the two most gram-negative bacteria and *Staphylococcus aureus*(Tyagi, Suryawanshi and Lalwani, 2002; Shitaye, 2008; Maramba-lazarte *et al.*, 2011; Units *et al.*, 2012; Khan *et al.*, 2012; Dagnew *et al.*, 2013; Jyothi *et al.*, 2013; Adugna Negussiea *et al.*, 2016; Lamba *et al.*, 2016; Hanumantha and Tabaseera, 2017; J. *et al.*, 2017) and *Coagulase-negative staphylococci(CONS*) (Tyagi, Suryawanshi and Lalwani, 2002; Zakariya and Bhat, 2011; Units *et al.*, 2012; Care *et al.*, 2013; Dagnew *et al.*, 2013; Jyothi *et al.*, 2013; Aamir, M and Ali, 2015; Adugna Negussiea *et al.*, 2016;) are the two common gram-positive microbes causing neonatal sepsis.

Studies in Ethiopia, despite their difference in the age range in the study population including neonatal sepsis used, at two university hospitals, Black lion and Gondar, revealed that the common pathogens were *Klebsiella* and *Escherichia coliform* gram-negative while *Staphylococcus aurous* and *Coagulase-negative staphylococci (CONS)*from gram-positive pathogens(Shitaye, 2008; Dagnew *et al.*, 2013). The study done in Black lion Specialized hospital indicated that 74.0% of all culture-proven sepsis was caused by these four bacteria *Klebsiella*(37.0%), *Staphylococcus aurous(22.2%), Escherichia coli(7.4%)* and *Coagulase-negative staphylococci (CONS)((7.4%)]*(Shitaye, 2008). The second study in Gondar University specialized hospital shows that 86.1% of all culture-proven sepsis has resulted from these microbes with the rate of *Coagulase-negative staphylococci (CONS)(42.3%)Staphylococcus aureus(23.9%), Klebsiella(12.9%)* and *Escherichia coli(7.0%)*(Dagnew*et al.*, 2013).Two studies reported that fungal pathogens were identified in neonatal sepsis in developing counties(Care *et al.*, 2013; Aamir, M and Ali, 2015)

2.4. Associated factors for mortality of NS

The literature agrees that an awareness of the many risk factors associated with neonatal sepsis prepares the clinician for early detection and effective treatment, thereby reducing mortality and morbidity(Aggarwal*et al.*, 2001; Vrishali Avinash Muley, Ghadage and Arvind Vamanrao Bhore, 2015). Accordingly, in different parts of the world including developing and developed countries researches identified risk factors for mortality of neonatal sepsis such as a study done in Brazilian Intensive Care Unit Mortality was higher among VLBW neonates (Freitas *et al.*, 2019).Studies identified that multiple births, mothers who did not attend antenatal care visits, neonates born by cesarean section, neonates not initiated breast feeding within 1 h of birth(Afif*et al.*, 2013; Debelew, Afework and Yalew, 2014; Bunduki and Sarkodie, 2019),prematurity, low birth weight(Dessu*et al.*, 2020) preterm delivery, sub-optimal birth weight ,early onset sepsis and having a length of stay greater than five days in the hospital are risk factors for mortality in (Atif M, Zia R, Malik I, et al., 2021))

2.5 Length of hospitalization in NS

The duration of empirical antibiotic therapy in neonates should be 48–72 hours pending culture results for suspected sepsis. Until further evidence, the current recommendation of 10–14 days of antimicrobial treatment is appropriate for blood-culture-positive sepsis without meningitis(Tewabe *et al.*, 2017). Studies identified that majority of the patients were admitted and stayed in the hospital for less than five days(Woday*et al.*, no date; Ginenus Fekadu1*, 2019; Dessu *et al.*, 2020).Having prolonged hospital stay brings other hospital acquired infection, development of microbial resistance which will increase cost of treatment(WHO, 2020).

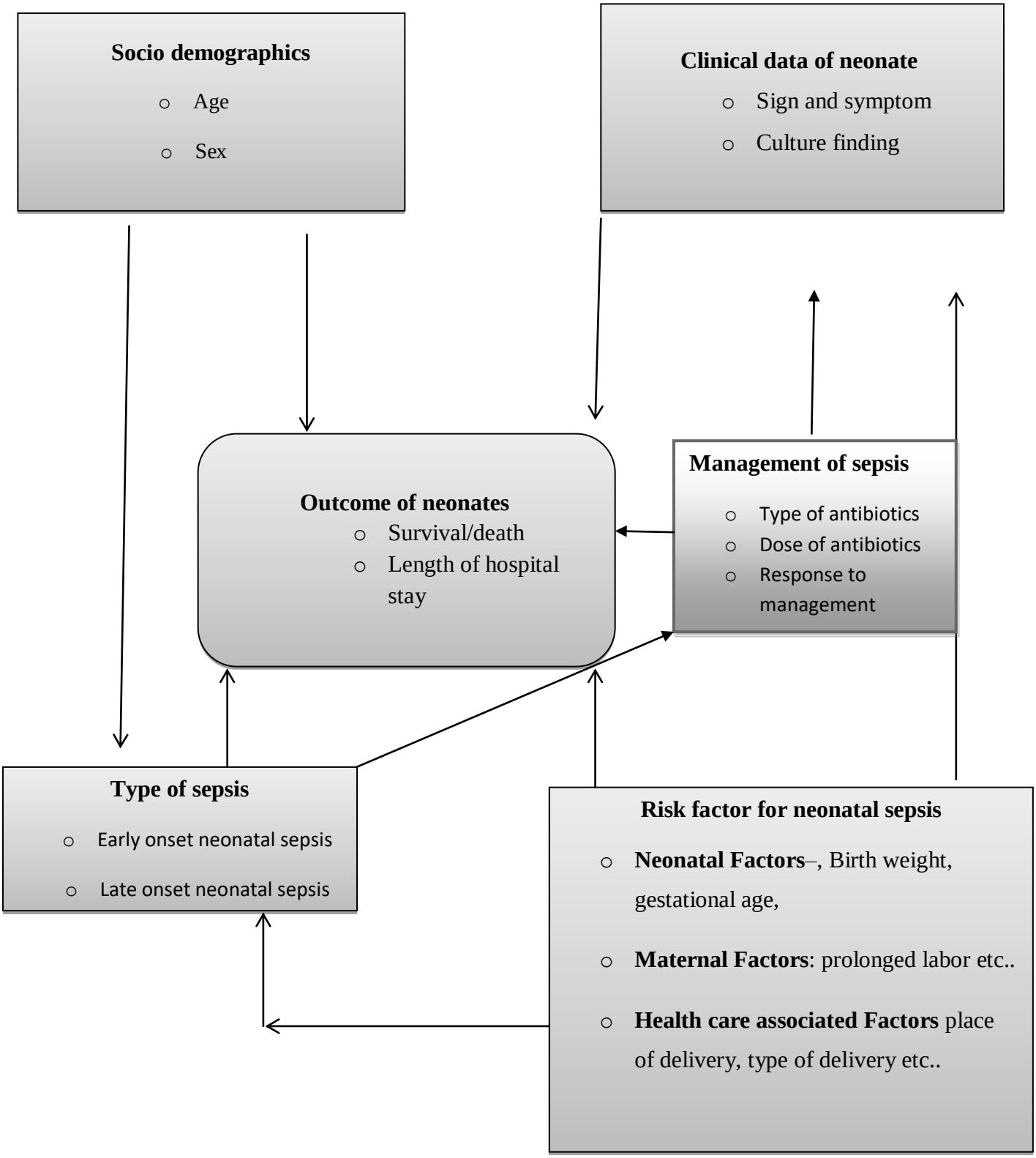


Figure 1 Conceptual framework

3. Objective

3.1. General Objective

- To assess treatment outcome of neonatal sepsis and associated factors among neonates treated at NICU of TASH, Addis Ababa, Ethiopia.

3.2. Specific objectives

- To determine the treatment outcome of neonatal sepsis among neonates treated at NICU of TASH, Addis Ababa, Ethiopia.
- To assess factors associated with mortality of neonatal sepsis among neonates treated at NICU of TASH, Addis Ababa, Ethiopia.
- To assess factors associated with length of hospitalization among neonates treated for neonatal sepsis at the NICU of TASH, Addis Ababa, Ethiopia.

4. Methodology

4.1. Study Setting

The study was conducted at Tikur Anbessa Specialized Hospital (TASH) which is tertiary specialized hospital in Ethiopia that gives service to the community in general. The hospital has around 465 physicians', 76 pharmacists, 992 nurses, and 115 other health care professionals dedicated to providing health care services. The major departments available in the hospital are internal medicine, emergency medicine, surgery, gynecology and obstetrics, pediatrics, oncology/chemo-radiology, radiology, psychiatry, and dermatology. The pediatric department has six major wings: Emergency admission services, Neonatal Intensive Care Unit(NICU), Pediatric intensive care unit ICU (PICU), under five admission unit, over five years admission unit and pediatric surgical admission unit. There are around 160-200 monthly neonatal admissions; the NICU has 60 beds (Asmare*et al.*, 2019)

4.2. Study Design and Period

A retrospective cohort study was conducted among admitted neonates from September, 2018 to September, 2020.

4.3. Source Population

All neonates with the possible serious bacterial infection (PSBI) diagnosis by the attending physician either clinically or laboratory-confirmation of neonatal sepsis during the study period and admitted at NICU ward of TASH were the source population of the study.

4.4. Study Population

Those neonates who fulfill the inclusion criteria and admitted at NICU during the study period were taken as the study population.

4.5. Eligibility Criteria

4.5.1. Inclusion Criteria

- All neonates (≤28 days), who were admitted to TASH at the NICU and neonates diagnosed with sepsis by the attending physician either clinically or laboratory-confirmation from September, 2018 to September, 2020.
- Medical record has complete information

4.5.2. Exclusion Criteria

- Neonates who were left against medical advice and referral to another hospital
- Those diagnosed with PNA, MAS, TGA, RD, surgical etc....
- Treated for < 2day

4.6. Variables

4.6.1. Dependent Variables

- Treatment outcome of NS (Death /Survived)
- Length of hospital stay (≤ 7days and > 7 days)

4.6.2. Independent Variables

- Socio-demographic characteristics including Age, Sex and Residence
- Clinical characteristics including neonatal factors: Birth weight, Gestational age; Maternal factors: Prolonged labor; Healthcare-associated factors, Mode of delivery; Clinical presentation at admission Hypothermia or Fever, Lethargy, Refusal to suck, Poor perfusion, Brady/Tachycardia, and Hypo/Hyperglycemia.

4.7. Sampling Technique and Sample Size Determination

The sample size was determined by using Open Epi-info version 3.03, by assuming caesarean section as exposed and spontaneous vaginal delivery as unexposed group of neonates. Considering a 95% level of confidence interval and 80% power was taken from the previous study done in Ethiopia(Orsido, Asseffa and Berheto, 2019), the sample size computed was 206 (137=SVD and 69=CS)(Figure 2) and data was collected by using systematic random sampling method using (Total of 691 neonates)K= 691/137= 5 for SVD and K= 691/69= 10

The 1st chart was selected randomly and every 5 for SVD and every 10 for CS of medical charts was taken until the required amount of sample size achieved.

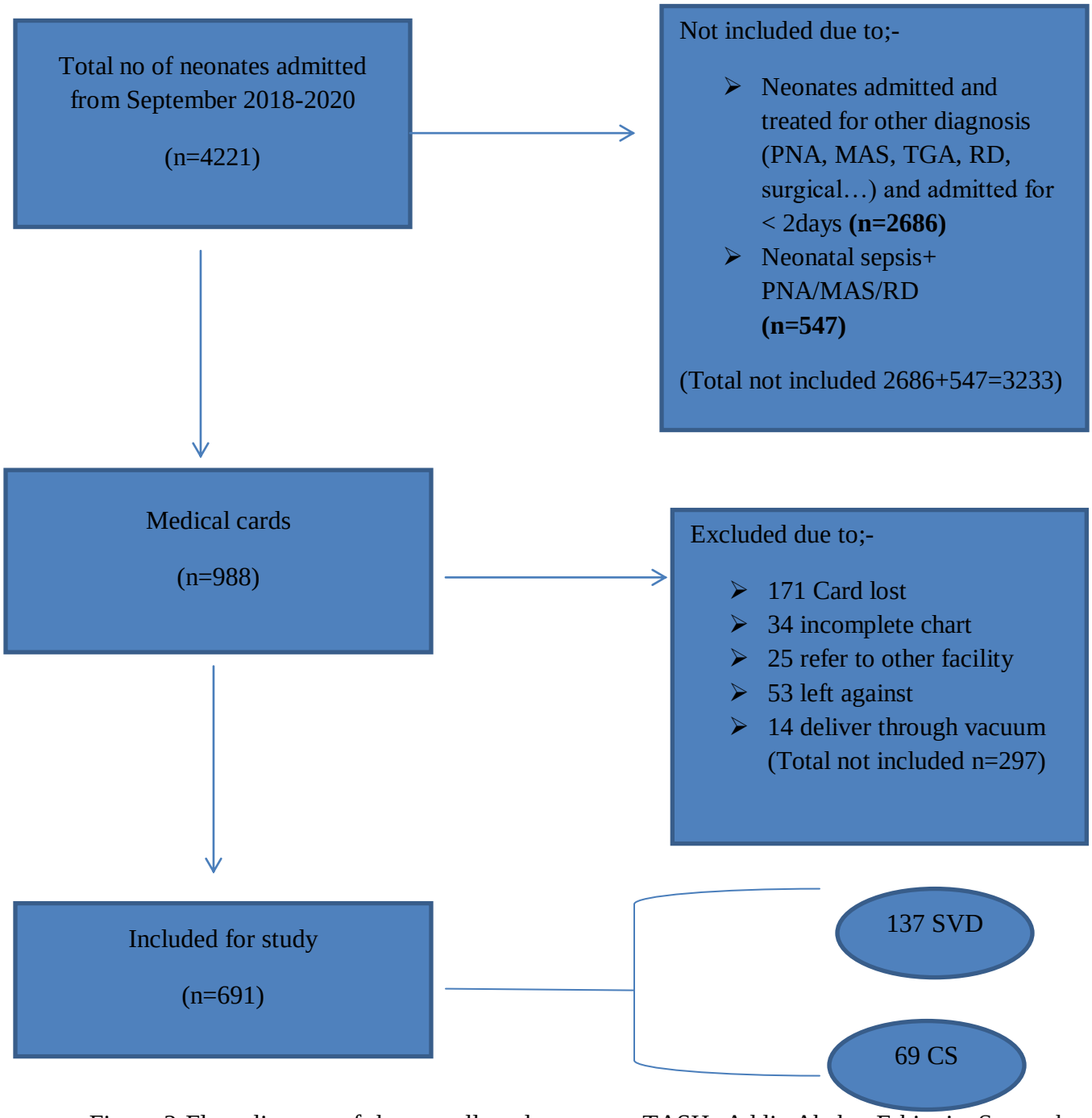


Figure 2 Flow-diagram of the overall study process, TASH, Addis Ababa, Ethiopia, September 2018to September, 2020.

4.8. Data Collection Instrument

Data on socio-demographic characteristics ,clinical characteristics, diagnostic of neonatal sepsis, treatment characteristics, and outcome was collected using a structured questionnaire (Annex I).The questionnaire was adapted from other similar studies and was prepared in English(Tewabe *et al.*, 2017; Freitas *et al.*, 2019; Orsido, Asseffa and Berheto, 2019).

4.8.1. Data Quality Assurance

To ensure the quality of data quality control activities were implemented, including a pre-test which was done before data collection at Ras Desta Hospital on 10% of the total sample size. After the pretest, modification was done meagerly on the clinical characteristics and diagnosis of neonatal sepsis. The outcome was evaluated based on clinical features, vital signs, laboratory investigations, and patient summary notes. During the study period, the patients were retrospectively followed for the occurrence of outcomes. Two BSC nurses working at NICU ward were data collecters.These were conducted using standardization of procedures and provide training for data collectors. A continuous follow up was undertaken by the principal investigator throughout the data collection period and the accuracy and completeness of the data were checked before entry of the data.

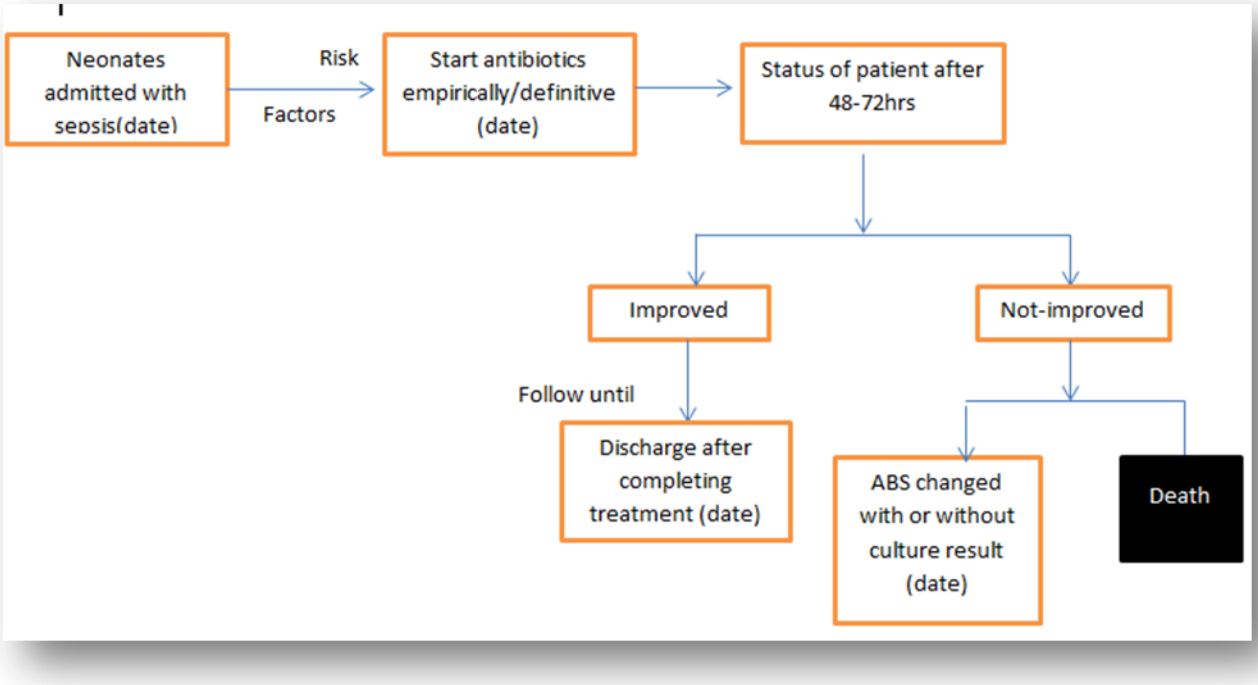


Figure 3 Data collection process of study participant recruitment process of patients attending in NICU wards of TASH

4.8.2. Data Entry and Statistical Analysis

For data entry and analysis, version 25 Statistical package for the social science (SPSS) was used. Descriptive statistics was used to summarize the data. Survival was estimated using the Kaplan-Meier method. Comparison between survival curves was made by employing the log-rank test. Cox regression analysis was used to calculate hazard ratio to identify risk factors for mortality. Univar ate Cox-regression analysis was used to determine association of different variables with survival. Variables with p-value less than 0.2 in crude model were included in the final cox proportional hazards regression model. Proportional hazard (PH) assumptions were initially tested for each model using log-log plot. Convergence, divergence or crossing of log-log plots will violates PH assumptions. The lines of log-log plot are parallel, so PH assumptions are not violated. So, proportional hazards are assumed. Variables with p-value less than 0.2 in crude model were included in the Cox proportional hazards regression model. For predictive factors associated with length of hospitalization, logistic regression was employed. A *p*-value of less than 0.05 in multivariable analysis was considered statistically significant.

4.9. Ethical Consideration

Before the start of the study, ethical clearance was obtained from Addis Ababa University Ref No. (ERB/SOP/201/02/2020), School of Pharmacy ethical review committee as well as permission was taken from the NICU ward of TASH. Confidentiality and anonymity of subject was maintained by not recording identifying details, such as name or any other personal identifiers. Only numerical identifications used as a reference. No disclosure of any name of the patients, the healthcare provider or drug product will be made in relation to the findings.

4.10. Operational Definition

- Neonatal sepsis ;- Infection involving bloodstream in newborn infants≤28 day (Tewabe et al, 2017, Fekadu et al,2019)
- Survived;-There was no death rescored at time of data collection
- Treatment outcomes of neonatal sepsis: - Defined as either survived or death
- Length of hospitalization:-Defined as early ≤7 days of hospitalization and late for >7days of hospitalization

5. Results

5.1. Socio-demographic Characteristics

A total of 206 neonates in this study, of which, majority (56.8%) of them were males and most (91.7%) of them were under the age of seven days. The mean (±SD) neonatal age was 2.63(±1.21) days. A significant number of neonates 91(44.2%) had low birth weight (<2.5kg). Most of them were 177(85.9%) residing in the urban and almost all of study participants 200(97.1%) had attended ANC. More than half (51.9%) of neonates were born in hospitals and were term 120 (58.3%) (Table 1)**.**

Table 1.Socio-Demographic Characteristics of Neonates Admitted to TASH, NICU, Addis Ababa, Ethiopia (n=206)

Variable	Category	SVD Frequency	CS Frequency	Total (Percentage)
Gender	Male	82	35	117(56.8)
	Female	55	34	89(43.2)
Age at admission(days)	0-7	125	64	189(91.7)
	8-28	12	5	17(8.3)
Birth weight (kg)	Normal birth weight	70	40	110(53.4)
	Low birth weight	62	29	91(44.2)
	Over weight	5	0	5(2.4)
Residence	Rural	15	14	29(14.1)
	Urban	122	55	177(85.9)
Birth level of Neonates	Para 1	85	40	125(60.7)
	Para 2	24	18	42(20.4)
	Para 3	16	8	24(11.7)
	Para 4	9	1	10(4.9)
	Para >4	3	2	5(2.4)
History of prenatal follow up	Yes	132	68	200(97.1)
	No	5	1	6(3.0)
Place of delivery	Hospital	47	60	107(51.9)
	Health center	76	8	84(40.8)
	Clinic	12	1	13(6.3)
	Other	2	0	2(1.0)
Gestational age	Term	79	41	120(58.2)
	Preterm	56	24	80(38.8)
	Post term	1	4	5(2.4)
	Unknown	1	0	1(0.5)

5.2. Maternal Risk Factors for Neonatal sepsis

Sixty(29.1%) out of 69 neonates delivered though CS had labor that lasted less than 18 hours and 32(15.5%) mothers had experienced Premature Rupture of Membrane (PROM). Most of the mothers 200(97.1%), 190(92.2%) had no history of UTI and febrile history, respectively. Chorioamnionitis was highly seen on those delivered through CS than SVD. (Table 2).

Table 2.Maternal Risk Factors for Neonatal Sepsis Admitted to TASH, NICU, Addis Ababa, Ethiopia (n=206).

Variable	Category	SVD Frequency	CS Frequency	Total (percentage)
Labor duration(in hours)	</=18	114	60	174(84.5)
	>18	21	9	30(14.6)
	Unknown	2	0	2(1.0)
Prolonged Rupture of Membrane	Yes	46	32	78(37.9)
	No	88	36	124(60.2)
	Unknown	3	1	4(2.0)
Urinary Tract Infection during delivery	No	132	68	200(97.1)
	Unknown	5	1	6(2.9)
Discharge during pregnancy	Yes	5	5	10(4.9)
	No	127	63	190(92.2)
	Unknown	5	1	6(3.0)
Febrile History of mother	Yes	6	4	10(4.9)
	No	126	64	190(92.2)
	Unknown	5	1	6(3.0)
History of Chorioamnionitis	Yes	9	8	17(8.3)
	No	123	60	183(88.8)
	Unknown	5	1	6(2.9)

5.3. Clinical Presentation of Neonatal Sepsis

The majority of neonates 172(83.5%) had no history of previous hospital admission. One hundred forty seven (71.4%) of them had EONS .While fifty two (25.24%) had co morbid illness in addition to neonatal sepsis; the commonest co morbid condition was EONS plus neonatal jaundice 24(11.7%). The most frequently identified sites of infection were CNS and chest focus 40(19.4%) and 31(15%) respectively **(Table 3).**

Table 3.Clinical Presentation of NS TASH, NICU, Addis Ababa, Ethiopia (n=206).

Variable	Category	SVD Frequency	CS Frequency	Total (percentage)
Previous hospital admission of neonate	Yes	25	9	34(16.5)
	No	112	60	172(83.5)
Co morbid illness	Yes	37	15	52(25.2)
	No	100	54	154(74.8)
Current diagnosis	EONS	95	52	147(71.4)
	EONS+ Neonatal jaundice	17	7	24(11.7)
	LONS	7	3	10(4.9)
	Others*	18	7	25(12.1)
Type of sepsis	EONS	125	64	189(91.7)
	LONS	12	5	17(8.3)
Focus of infection	Central Nerves System	32	8	40(19.4)
	Gastro intestinal	4	1	5(2.4)
	Chest	22	9	31(15.0)
	Central Nervous System +Chest	4	1	5(2.4)
	Not recorded	75	50	125(60.7)
*Others**	EONS+Opthalmic Neonatorum; EONS +Left renal mass? Multi cystic Dysplasia kidney; EONS+ Neonatal Seizure; EONS+?Congenital pneumonia; EONS+HBV; EONS+RVI; EONS+AKI; EONS+CongenitalHypothyrodism; EONS+Micropenus+Undestended testis; EONS+HAI+?Aspiration pneumonia+N,Jaundise; EONS+HAI+N.Jaundise; EONS+ Pre renal azotemia+Hypothyrodism+HAI; EONS+Down syndrome; LONS+N.seizure; LONS+Complex CHD; LONS+SCAP; LONS+HAI			

5.4. Laboratory Results of Neonates with Sepsis

During the study period a total of 62 (30.1%) cultures were sent and more than half of them (n=41) were sent after antibiotic was started. *K,pneumonia* mainly seen on those delivered through SVD.(Table 4)

Table 4. Laboratory Results of Neonates with Sepsis admitted to TASH, NICU, Addis Ababa, Ethiopia (n=206).

Variable	Category	SVD Frequency	CS Frequency	Total (percentage)
Site of sample collection	Blood	18	17	35(17.0)
	CSF	11	2	13(6.3)
	Blood +CSF	20	4	24(11.7)
	Not send	84	46	130(63.1)
	Others *	4	0	4(1.9)
Culture and gram stain	Not send	118	26	144(69.9)
	Send	48	14	62(30.1)
Time of sample collection	Before antibiotics started	24	11	35(17)
	After antibiotics started	29	12	41(19.9)
Culture and gram stain result	Gram positive	2	0	2(1.0)
	Gram negative	7	1	8(3.9)
	Contaminant	2	0	2(1.0)
Specific pathogen	*K,pneumonia*	5	1	6(2.9)
	E,coli	1	0	1(0.5)
	Acitinobacteracia	1	0	1(0.5)
	MRSA	1	0	1(0.5)
	Enterobacteracia +K,pneumonia	1	0	1(0.5)

**Others*: Wound, eye discharge

5.5. Clinical symptoms of Neonatal Sepsis among neonates admitted at TASH

Forty eight (23.3%) neonates delivered by SVD were experiencing poor feeding status, while those delivered through CS had fever of 22(10.7%) being the most common symptoms among the study participants (Table 5).

Table 5.Clinical symptoms of neonatal sepsis among neonates admitted at TASH, Addis Ababa, Ethiopia, n=206.

Variable	Category	SVD Frequency	CS Frequency	Total (percentage)
Fever	Yes	41	22	63(30.6)
	No	96	47	143(69.4)
Respiratory feature	Tachypnea	24	13	37(17.9)
	Flaring and granting	2	0	2(1.0)
	Retraction	5	3	8(3.9)
	Irregular respiration	1	1	2(1.0)
	More than one symptom	39	12	51(24.8)
	No respiratory feature	66	40	106(51.5)
Gastro Intestinal	Poor feeding	48	19	67(32.5)
	Vomiting	6	5	11(5.3)
	Abdominal distension	0	2	2(1.0)
	More than one symptom	63	41	104(50.5)
	No symptom	20	2	22(10.7)
Neurological feature	Decreased activity/Lethargic	14	4	18(8.7)
	Irritability	11	8	19(9.2)
	Tremor/Seizure	2	1	3(1.5)
	More than one symptom	103	56	159(77.2)
	No symptom	7	0	7(3.4)
Metabolic feature	Normal	11	3	14(6.8)
	Hypoglycemia	4	10	14(6.8)
	Hyperglycemia	1	0	1(0.5)
	Not done	121	56	177(85.9)

5.6. Pattern of Antibiotic Use for Treatments of NS

Antibiotics were prescribed empirically among 61.6% (127) of the neonates delivered through SVD for the treatment of sepsis (Figure 4). The combination of ‘Ampicillin + Gentamicin' 168 (81.6%) was the most commonly prescribed antibiotic, followed by ‘Ampicillin + ceftriaxone' 27(13.1%) (Figure 5). Regarding the doses of antibiotics Ampicillin 25-50mg/kg/dose in 151(75.3%), Gentamicin 4mg/kg/day in 132(64.1%) of neonates, while Cefotaxime 50-75 mg/kg/dose was prescribed in 27(13.1%) (Table 6).

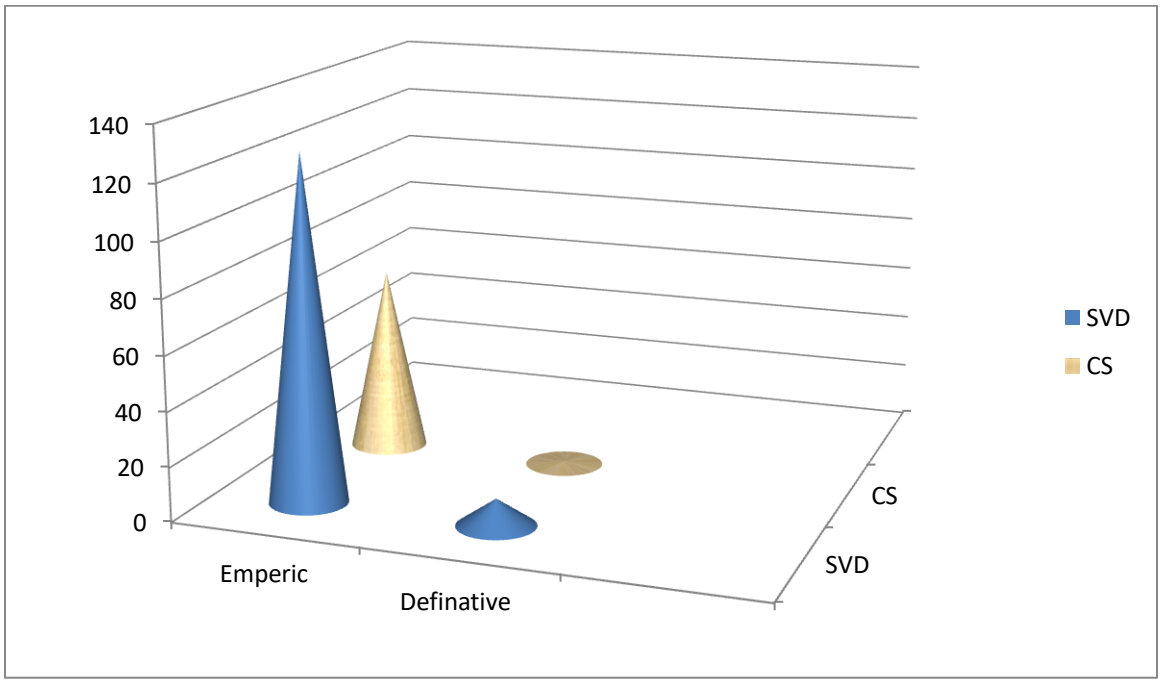
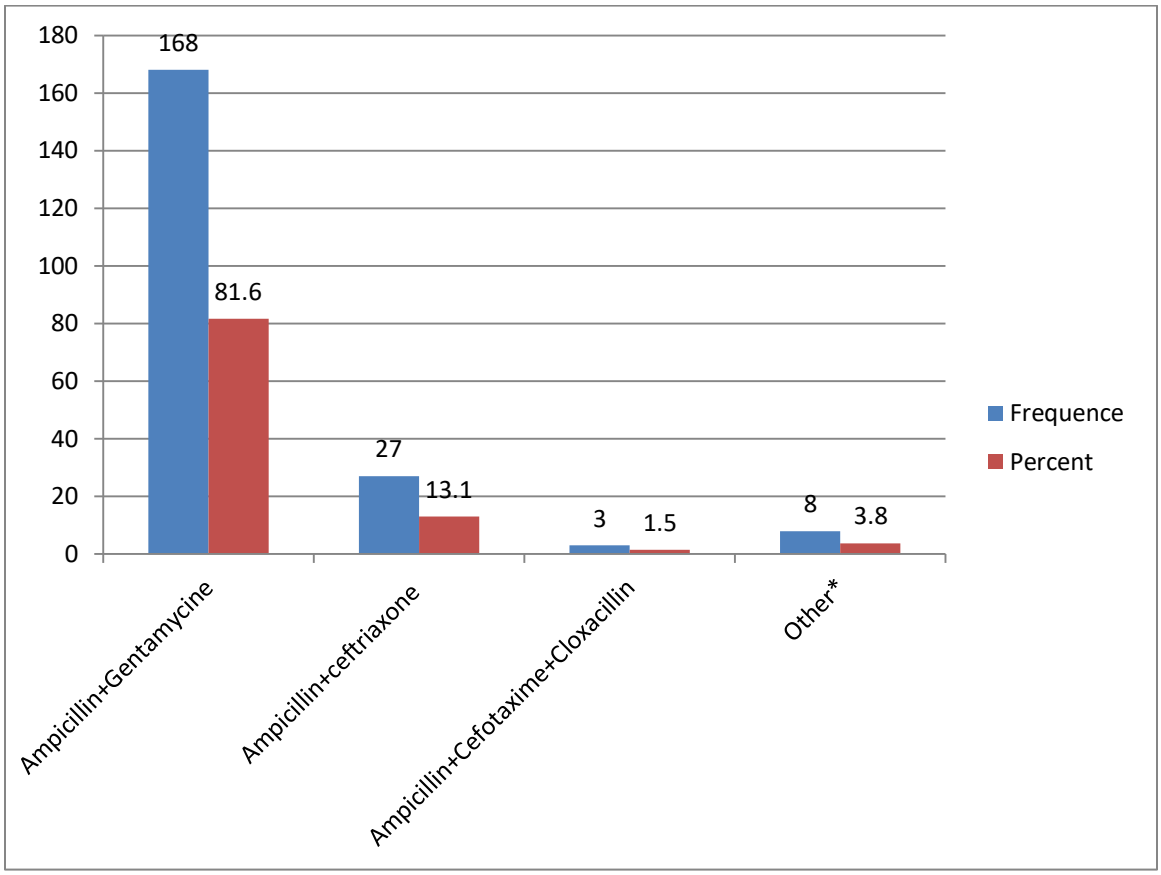


Figure 4.Patterns of antibiotics used for treatment of NS



*Other**Ampicillin+Gentamycine+Metrindazol; Ampicilin+Ceftriaxone;Cefepime+vancomycin; Cefepime+Vancomycine+Metrindazole; Ceftraiaxone+Azitromycine; Ceftraiaxone+Gentamycine

Figure 5.Percentage of Medication regimens given for neonatal sepsis patients admitted to TASH, Addis Ababa, Ethiopia, 2021

Table 6. Pattern of antibiotic use of Neonates with Sepsis admitted to TASH, NICU, Addis Ababa, Ethiopia (n=206).

Variable	Category	Frequency (percentage)
Ampicillin dose given	25-50mg/kg/dose	151(73.3)
	51-75mg/kg/dose	22(10.7)
	76-100mg/kg/dose	28(13.6)
	Not given	5(2.4)
Gentamicin	<3mg/kg/day	11(5.3)
	3mg/kg/day	29(14.1)
	4-5mg/kg/day	132(64.1)
	Not given	34(16.5)
Cefotaxime	50-75mg/kg/dose	27(13.1)
	76-100mg/kg/dose	21(10.2)
	Not given	158(76.7)
Ceftriaxone	50-75mg/kg/day	1(0.5)
	76-100mg/kg/day	3(1.5)
	Not given	202(98.1)
Cefepime	30mg/kg/dose	5(2.4)
	50mg/kg/dose	6(2.9)
	Not given	195(94.7)
Ceftazidime	30mg/kg/dose	2(1.0)
	Not given	204(99)
Cloxacillin	25-50mg/kg/day	3(1.5)
	Not given	203(98.5)
Vancomycin	15-20mg/kg/day	1(0.5)
	30mg/kg/day	6(2.9)
	40-60mg/kg/day	6(2.9)
	Not given	193(93.7)
Metronidazole	7.5-15mg/kg/day	2(1.0)
	15-30mg/kg/day	6(2.9)
	Not given	198(96.1)

Azithromycin	10mg/kg/day for 3 days	1(0.5)
	10mg/kg/day for 5 days	2(1.0)
	Not given	203(98.5)
Meropenem	20-30mg/kg/day	6(2.9)
	40mg/kg/day	4(1.9)
	Not given	196(95.1)

5.7. Neonates Progress after Starting of Treatment

The mean (±SD) of length of hospital stay at the NICU was 8.92(±6.18) days. In most of the neonates 171 (83.0%), the course of antibiotics was not changed throughout their treatment. At the end of discharge out of one hundred thirty seven, 128 (62.3%) were survived on those neonates delivered through SVD (Table 7).

Table 7. Progress of neonate with Sepsis admitted to TASH, NICU, Addis Ababa, Ethiopia (n=206).

Variable	Category	SVD (Frequency)	CS (Frequency)	Total (percentage)
End of discharge clinical status	Survived	128	65	193(93.7)
	Death	9	4	13(6.3)
Clinical condition of neonates after 48-72 hours of Antibiotics	Improved	107	57	164(79.6)
	Worsened	30	12	42(20.4)
Course of antibiotics	Not changed	110	61	171 (83.0)
	Changed	23	12	35 (17.0)
Antibiotic change	To Ampicillin+Ceftotaxime	5	5	10(4.8)
	To Cefepime+Vancomycine	7	3	10(4.8)
	To Meropenum	6	4	10(4.8)
	To Cefepime+Vancomycine+Metrindazol	1	0	1(0.5)
	Add Metronidazole	2	0	2(1.0)
	To Vancomycin	2	0	2(1.0)
Antibiotic dose change	No	132	64	196(95.1)
	Dose increased/decreased	5	5	10(4.8)
Total duration of antibiotics	3-5days	53	33	86(41.7)
	6-10days	49	29	78(37.8)
	11-15days	15	3	18(8.7)
	16-21days	11	2	13(6.3)
	>21 days	9	2	11(5.3)
Length of hospital stay	</=7days	80	49	129(62.6)
	>7days	57	20	77(37.4)

5.8. Cox Proportional Hazard Regression Model

The univariate analysis, Cox proportional hazard regression reveled that variables such as female gender, focus of sepsis with focus of chest and CNS, worsen clinical outcome after 72 hours of antibiotics and Ampicillin 76-100 mg/kg/dose were associated with increased risk/hazard of death. On the contrary neonates without PROM, SVD mode of delivery Meropenum 40 mg/kg/8hours, and neonates for whom antibiotics dose was increased on the initial treatments were associated with lower risk of mortality..

The multivariate analysis revealed that pregnant women with history of vaginal discharge has 5.486 higher risk of having neonatal mortality compared to pregnant women without discharge (AHR, 5.486, 95% CI: 1.308-26.134). On the other hand, absence of PROM (0.503 CI: 0.326-0.776) and those neonates delivered through SVD (AHR 0.265, CI: 0.091-0.767), were associated with decreased risk of mortality. Kaplan-Meier survival analysis using log-rank test ($p = 0.014$) revealed that there is a statistically significant survival difference between those neonates delivered through SVD than neonates delivered by CS (Figure 5).

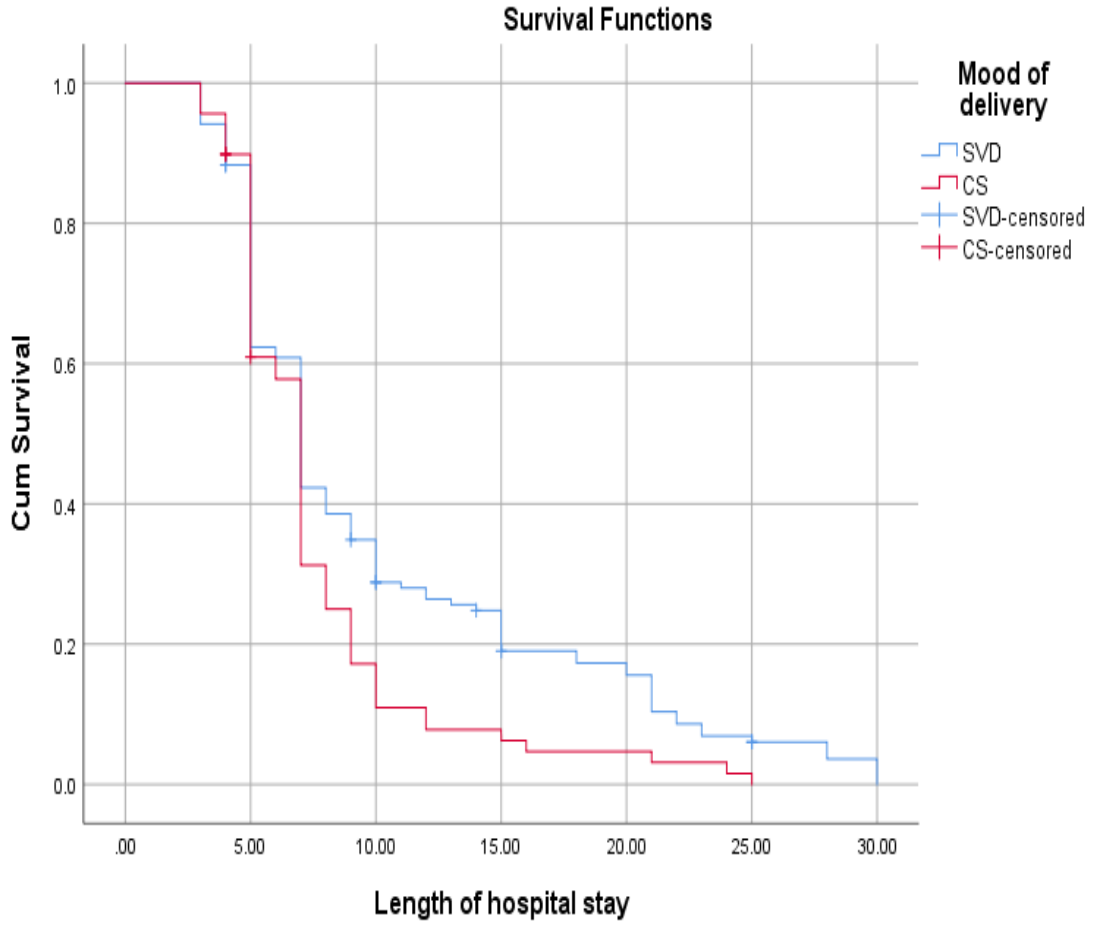


Figure 6.Kaplan-Meier survival analysis curve in CS delivered neonates and SVD delivered neonates

Table 8. Cox hazard regression model of neonates admitted to TASH, NICU, Addis Ababa, Ethiopia (n=206)

Variables	Clinical outcome		CHR (95%CI)	AHR (95%CI)	P-value
	Survived	Death			
Gender					
Male	109(52.9)	8(3.9)	1.00		
Female	84(40.8)	5(2.4)	1.653(1.227-2.227)	1.515 (0.988-2.298)	0.051
Age category					
<7 days	177(85.9)	12(5.8)	1.00		
>7 days	16(7.8)	1(0.5)	0.775 (0.463-1.300)	1.203 (0.304-4.759)	0.792
PROM					
Yes	76(36.9)	2(0.9)	1.00		
No	117(56.8)	11(5.3)	0.512 (0.304-0.748)	0.509 (0.306-0.786)	**0.009***
Discharge during pregnancy					
No	180(87.4)	10(4.9)	1.00		
Yes	9(4.4)	1(0.5)	1.389 (0.710-2.719)	5.486(1.308-26.134)	**0.021***
Unknown	4(1.9)	2(0.9)	0.924 (0.284-3.005)	8.686 (0.448-1.624)	0.431
Mood of delivery					
CS	65(31.6)	4(1.9)	1.00		
SVD	128(62.1)	9(4.7)	0.488 (0.228-1.043)	0.265 (0.091-0.767)	0.014*
Focus of infection					
CNS	37(17.9)	3(1.5)	1.00		
GI	3(1.4)	2(0.9)	1.061 (0.322-3.491)	0.471 (0.040-5.575)	0.551
Chest plus CNS	4(1.9)	1(0.5)	1.707 (1.008-2.891)	0.333 (0.052-2.133)	0.246
Not recorded	124(60.2)	1(0.5)	1.273 (0.447-3.629)	1.438 (0.118-17.50)	0.776
Site of sample collection					
Blood	34(16.5)	3(1.5)	1.00		
CSF	15(7.3)	1(0.5)	0.793 (0.461-1.690)	0.347 (0.071-1.332)	0.315
Blood plus CSF	21(10.2)	2(0.9)	0.682 (0.327-1.036)	0.301 (0.036-1.114)	0.086
Not send	123(59.7)	7(3.4)	1.826 (1.193-2.796)	1.046 (0.568-1.827)	0.884
Neonatal fever					
Yes	60(29.1)	3(1.5)	1.00		
No	133(64.6)	10(4.9)	0.729 (0.529-1.004)	0.954 (0.534-1.671)	0.845

Presence of GI symptoms					
Yes	93(45.1)	9(4.4)	1.00		
No	100(48.5)	4(1.9)	1.466 (0.693-1.961)	1.837 (0.624-2.921)	0.927
Presence of Neurological features					
Yes	41(19.9)	6(2.9)	1.00		
No	152(73.8)	7(3.4)	0.311 (0.077-1.251)	0.120 (0.005-2.910)	0.193
Metabolic features					
Normal(25-7mmol/l)	13(6.3)	1(0.5)	1.00		
Hypoglycemia (<2mmol/l)	11(5.3)	3(1.5)	1.844 (0.812-4.190)	1.645 (0.462-5.885)	0.442
Hyperglycemia (>7mmol/l)	1(0.5)	1(0.5)	2.710 (0.346-21.25)	1.135 (0.117-11.01)	0.442
Unknown	168(81.5)	8(4.4)	1.355 (0.765-2.400)	1.290 (0.543-3.062)	0.564
Ampicillin dose					
25-50 mg/kg/dose	142(68.9)	9(4.4)	1.00		
51-75 mg/kg/dose	20(9.7)	2(0.9)	1.115 (0.695-1.787)	1.548 (0.839-2.855)	0.162
76-100 mg/kg/dose	27(13.1)	1(0.5)	0.620 (0.404-0.952)	0.484 (0.155-1.506)	0.210
Not given	4(1.9)	1(0.5)	0.599 (0.220-1.633)	29.48 (2.094-415.1)	0.162
Cefotaxime dose					
50-75 mg/kg/day	22(10.7)	5(2.4)	1.00		
76-100 mg/kg/day	20(9.7)	1(0.5)	0.911 (0.494-1.681)	0.828 (0.207-3.305)	0.789
Not given	151(73.3)	7(3.4)	2.207 (1.385-3.185)	0.580 (0.076-4.428)	0.599
Cefepime dose					
<30 mg/kg/day	4(1.9)	1(0.5)	1.00		
35-50 mg/kg/day	3(1.4)	3(1.4)	0.415 (0.080-2.150)	0.028 (0.001-1.306)	0.068
Not given	186(91.7)	9(4.4)	3.037 (0.951-9.697)	1.011 (0.087-11.73)	0.993
Meropenum dose					
20-30 mg/kg/8hours	3(1.4)	3(1.4)	1.00		
40 mg/kg/8hours	3(1.4)	1(0.5)	0.296 (0.093-0.939)	0.115 (0.005-4.598)	0.281
Not given	186(91.7)	10(4.8)	0.255 (0.090-0.717)	3.739 (0.205-68.22)	0.373

Progress after 72 hours of antibiotics					
Improved	163(79.1)	1(0.5)	1.00		
Worsen	30(14.5)	12(5.8)	1.48 (0.087-0.252)	1.37 (0.019-1.007)	0.051
Antibiotics dose changed					
No	187(90.8)	9(4.4)	1.00		
Dose increased	6(2.9)	4(1.9)	0.322 (0.140-0.744)	1.143 (0.200-6.529)	0.880

*variables showed statistical significant association

5.9. Predictors of Length of Hospitalization

In the univariate analysis female gender, low birth weight, absence of co morbidity, having more than one GI symptoms, neonates with tremor/ seizure history, no treatment with Cefotaxime, neonates with worsen treatment outcome after 72 hours of antibiotics initiation and neonates increased their antibiotics dose from baseline treatment showed association to determine the length of hospitalization. However, upon multivariable analysis Low-birth weight (AOR =11.87, 95%CI: 2.344-60.15) and being on Ampicillin (AOR=16.09, CI: 4.484-57.74) were associated with prolonged hospitalization. On the other hand, being female (AOR= 0.090, 95%CI: 0.018-0.458); Absence of GI symptoms (AOR= 0.214, 95%CI: 0.19-0.350); and antibiotics dose change from initials treatment (AOR= 0.081, 95% CI: 0.001-0.703) were associated with a decreased rate of hospitalization.(Table 9).

Table 9.Predictors of Length of Hospitalization of neonates admitted to TASH, NICU, Addis Ababa, Ethiopia (n=206)

Variables	Length of hospitalization		COR (95% CI)	AOR (95% CI)	P-Value
	<7 days	>7days			
Gender					
Male	63 (30.6)	54 (26.2)	1.00		
Female	66 (32.0)	23 (11.2)	0.407 (0.224-0.739)	0.090 (0.018-0.458)	**0.004***
Birth weight					
Normal (2.5-4kg)	77(37.4)	33(16.0)	1.00		
Low (<2kg)	49(23.8)	42(20.4)	2.000 (1.120-3.571)	11.87 (2.344-60.15)	**0.003***
High (>4kg)	3(1.4)	2(0.9)	1.556 (0.248-9.747)	0.039 (0.774-7.662)	0.807
Mood of delivery					
SVD	80(38.8)	57(27.7)	1.00		
CS	49(23.8)	20(9.7)	0.573 (0.308-1.066)	0.233 (0.045-1.210)	0.083
Co morbidity					
Yes	21(10.2)	31(15.0)	1.00		
No	108(52.4)	46(22.3)	0.289 (0.150-0.554)	0.370 (0.064-2.127)	0.265
Types of sepsis					
Early onset	121(58.7)	68(33.0)	1.00		
Late onset	8(3.9)	9(4.4)	2.002 (0.738-5.429)	14.18 (0.046-4.427)	0.899
GI symptoms					
Poor feeding	33(16.0)	34(16.5)	1.00		
Vomiting	6(2.9)	5(2.4)	0.809 (0.225-2.909)	12.62 (0.644-247.5)	0.095
Abdominal distention	1(0.5)	1(0.5)	0.971 (0.058-16.16)	60.77 (0.098-37.62)	0.210
>1 symptom	74(35.9)	30(14.6)	0.393 (0.208-0.746)	0.627 (0.148-2.655)	0.526
No symptom	15(7.3)	7(3.4)	0.453 (0.164-1.125)	0.214 (0.19-0.350)	**0.000***

Neurological features					
Decreased activity/Lethargy	8(3.9)	10(4.9)	1.00		
Irritability	6(2.9)	13(6.3)	1.293 (0.397-2.882)	0.948 (0.020-46.07)	0.979
Tremor/Seizure	1(0.5)	2(0.9)	0.346 (0.129-0.930)	4.231 (0.475-2.168)	0.557
>1 symptom	111(53.9)	48(23.3)	0.600 (0.103-3.495)	0.155 (0.007-3.441)	0.239
Metabolic features					
Normal (25-7mmol/l)	6(2.9)	8(3.9)	1.00		
Hypoglycemia (<2mmol/l)	10(4.8)	3(1.5)	0.300 (0.062-1.442)	0.169 (0.003-8.645)	0.376
Hyperglycemia (>7mmol/l)	1(0.5)	1(0.5)	1.544 (0.417-1.332)	8.264 (0.422-1.946)	0.621
Unknown	112(54.4)	65(31.5)	0.435 (0.145-1.301)	0.736 (0.041-13.17)	0.835
Ampicillin dose					
25-50 mg/kg/dose	103(50.0)	48(23.3)	1.00		
51-75 mg/kg/dose	15(7.3)	7(3.4)	1.001(0.383-2.616)	0.180 (0.015-2.128)	0.173
76-100 mg/kg/dose	9(4.4)	19(9.2)	4.530 (1.909-10.74)	16.09 (4.484-57.74)	**0.005***
Not given	2(0.9)	3(1.5)	3.219 (0.521-19.89)	5.562 (0.224-2.582)	0.849
Gentamicin dose					
<3 mg/kg/day	8(3.9)	3(1.5)	1.00		
3 mg/kg/day	17(8.3)	12(5.8)	1.882 (0.412-8.595)	5.642 (0.295-107.7)	0.250
	89(43.2)	43(20.9)	1.288 (0.325-5.100)	0.460 (0.028-7.481)	0.586

>3 mg/kg/day					
Not given	15(7.3)	19(9.2)	3.378 (0.762-14.98)	0.053 (0.118-102.2)	0.447
Cefotaxime dose					
50-75 mg/kg/day	9(4.4)	18(8.7)	1.00		
76-100 mg/kg/day	6(2.9)	15(7.3)	1.250 (0.362-4.318)	0.002 (0.447-1.161)	0.055
Not given	114(55.3)	44(21.4)	0.193 (0.081-0.462)	0.015 (0.487-14.49)	0.232
Progress after 72 hours of antibiotics					
Improved	120(58.3)	44(21.4)	1.00		
Worsen	9(4.4)	33(16.0)	10.00 (4.431-22.56)	17.02 (0.445-65.01)	0.128
Antibiotics dose changed					
No	125(60.7)	71(34.5)	1.00		
Dose increased/decreased	4(1.9)	6(2.9)	2.541 (0.721-9.621)	0.081 (0.001-0.703)	**0.040***

*variables showed statically significant association

6. Discussion

Neonatal sepsis is a common type of infection which is the major cause of admission in the neonatal ICU worldwide(Islam, Shahidullah and Akter, 2019). This study aimed to investigate the treatment outcomes, factors towards mortality of neonatal sepsis and the factors of length of hospitalization among neonates attending to TASH.

This study identified that 193(93.7%) of them successfully completed the treatment (i.e., discharged with treatment success), while 13(6.3%) died. Comparable result was found at study done Felege Hiwot; 189 (84%) (Tilahun Tewabe etal.2017),Public hospitals,Sumera and Afar Ethiopia 300 (76.7%)(Abay Woday,2021),Wollega university(276 (90.19%) ,(Ginenus Fekadu ,2019).While, Higher no of death was seen at Congo, 48 (21.1%) (Bunduki and Adu-Sarkodie (2019)),Pakistan 123 (21%) (Atif M, Zia R, Malik I, et al., 2021),Wolaita Sodo 159(16.5%),(Tujare Tunta Orsido 2019) and Mizan Tepi University,(Wale Alemnew, Chelkeba Legese,(68 (32.2%) .The difference might be due to difference in no of ANC visit (maternal status, difference in maternal and other risk factors ,also difference in study design and sample size.

In this study neonates with EONS were more likely to die than LONS. Similar finding was seen in study done at southeastern Mexico, Tanzania and WolaitaSodo University(Leal *et al.*, 2012; Mhada *et al.*, 2012; Orsido, Asseffa and Berheto, 2019).Having similar study design but different result was found in a study done in Brazil which shows Infants with LOS were more likely to die than EONS (Suppo et al., 2014; Bunduki and Sarkodie, 2019). This might be due to a high burden of LOS among neonates admitted to the NICU in Brazil and it might be also quality of care, such as;- Infrastructure constraints for the care of pregnant women and neonates. Definition for early and late sepsis are differ from set up to set up and delayed diagnosis, and poor management of infection might be the reason.

This study revealed that mothers delivered by SVD had 74% protective effect on risk of neonatal mortality compared to CS. On the contrary study at WolaitaSodo University Teaching and referral hospital shows neonates born through cesarean section had a 66% lower risk of death as compared with spontaneous vaginal delivery (SVD) AHR [95%CI] 0.34[0.19–0.61] (Orsido, Asseffa and Berheto, 2019). The possible explanation might be due to time of delivery, complicated status of the pregnant women during transfer for C/S to black lion hospital, which might contribute to the observed increased mortality among neonate delivered through CS.

The multivariate analysis revealed that pregnant women with history of vaginal discharge has about 5.486 higher risk of having neonatal mortality compared to pregnant women without discharge (AHR, 5.486 CI: 1.308-26.134). Similar study design done in Mexico showed prematurity and low birth weight are factors associated with mortality in newborns with sepsis(Leal *et al.*, 2012). While a study conducted at Pakistan and Samara University, shows preterm delivery , sub-optimal birth weight ,early onset sepsis and length of hospital stay remained significantly associated with neonatal death(Woday*et al.*, no date; Id *et al.*, 2021).A prospective cohort study conducted at Arbaminch General hospital, shows history of foul-smelling liquor, history of UTI/STI, history of intrapartum fever, and history of diagnosed chorioamnionitis were the variables, which had high effect on neonatal mortality among neonates with neonatal sepsis(Dessu*et al.*, 2020) This might be due to the different in independent variables and number of ANC follow ups.

Out of 206 neonatal septicemia cases 5.82% (n=12) had growth on blood culture. This finding was in line with some other studies. However, studies done in Philippines and Ethiopia showed a higher culture proven sepsis magnitude with 50% and 44.7% respectively(2,5,9–13).In this study gram negatives were the predominant pathogens identified, similar studies were found from developing counties in Asia, Middle east and Africa(El-din *et al.*, 2015; Pokhrel *et al.*, 2018; Yadav *et al.*, 2018; Islam, Shahidullah and Akter, 2019; Thapa, 2019) as opposite finding was obtained on 233 neonates in a study conducted in 2015 using a retrospective descriptive study design, carried out at the Special Care Baby Unit (SCBU) of the Niger showing 52 (53.6%) of the isolated organisms being Gram positive and 45 (46.4%) Gram negative and also a study conducted in India by Shipra Galhotra et al shows Gram positive isolates were more predominant as compared to Gram negative isolates(El-din *et al.*, 2015; Peterside, Pondei and Akinbami, 2015; Gupta *et al.*, 2016; Tsehaynesh *et al.*, 2017; Aku *et al.*, 2018). The possible explanation might be due to different microbiological pattern from country to country even from time to time and also its association with several risk factors(how culture was taken, difference in quality of laboratory procedure, and time of antibiotic started)

Current WHO guidelines recommend IM or IV Ampicillin and Gentamicin as first line in neonates with documented risk factors for infection for at least 2 days and to reassess. However, there has been an increased use of alternative protocols using a cephalosporin (most commonly Cefotaxime) or a glycopeptides (most commonly Vancomycin) as a first line option to treat especially late onset sepsis ,due to increased resistance among the most common pathogen such as Coagulase-negative staphylococcus. Ampicillin combined with a third-generation

cephalosporin agent (most commonly Cefotaxime) is also used as an alternative for early onset sepsis(FuchStatewidesa*et al.*, 2016; Korang *et al.*, 2019) Most of the patients in this study were treated by Ampicillin plus Gentamicin which was similar with studies done at Bishofitu General Hospital Debrezeit and Wollega (Minyahil Alebachew Woldu*1, Molla Belay Guta2, Jimma Likisa Lenjisa2, Gobezie Temesgen Tegegne2, 2014; Ginenus Fekadu1*, 2019). On the contrary a study done in Pakistan, most of the neonates received the combination of Amikacin and Cefotaxime at the start of treatment (Id *et al.*, 2021) This variation is due to difference in guideline, the pathogens causing neonatal infections and their antibiotic susceptibility patterns change over time and local antibiotic resistance of the most common pathogen. In our study taking meropenum dose of 40mg/kg/day reduces risk of mortality but it does not mean we have to use as first line but needs physician decision.

However, upon multivariate analysis neonates with low birth weight were about 11.87 times higher risk of having prolonged hospitalization than neonates with normal birth weight (AOR=11.87, CI: 2.344-60.15). Supported by Biniyam Sahiledengle et al Goba referral hospital, 2020)40% [AHR: 0.60, (95% CI: 0.40-0.90)], Seaton SE,et al,2016 systematic review. Because they are predisposed to different infection, respiratory distress, NEC,IVH etc.. as well when neonates are admitted in the hospital for a longer period they acquires new infection so that antibiotics might not work and even they develop resistance to the antibiotics so that affordability plus availability will be a challenge in the meantime the neonates will be died. Therefore, early detection of risky situations and appropriate practice of newborn care can halt the problem

7. Limitations of the Study

All the important information may not be recorded well or may not be available as expected example patients, when culture was send and collected, how many bottles are not well recorded. As well due to low culture positivity rates, determining the outcome with treatment was very challenging .Having small sample size might affect the power of test. The study area covers only TASH; its generalizability to all hospitals of the city and Ethiopia may not be possible and this might also decrease our precision.

8. Conclusions

In the present study the rate of survival was comparable with most of the studies conducted elsewhere. Pregnant mothers with history of discharge were associated with an increased hazards of neonatal mortality compared to pregnant women without discharge. On the other hand, neonates having a normal birth weight; absence of PROM and those neonates delivered through SVD were associated with decreased risk of mortality. Low birth weight and taking Ampicillin at a dose of 76-100 mg/kg/dose were associated with increase length of hospitalizations compared to neonates received at a dose of 25-50 mg/kg/dose. On the other hand, being female; absence of GI symptoms; and antibiotics dose change from initial treatment were associated with a decreased length of hospitalization.

9. Recommendation

The OBY/GYN department should promote delivery though SVD, and aggressively manage of pregnant women with vaginal discharge as it significantly affects the outcome of their newborns with neonatal sepsis. In addition emphasis should be given on meticulous management of neonatal sepsis and early change of antibiotics is imperative when needed as it reduces length of hospital stay thereby decreasing mortality. Further studies using strong designs like prospective study should be conducted to explore more maternal and neonatal mortality risk factors also factors for prolonged hospital stay.

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11. Annex

11.1. Annex I: Questioner

Questionnaire on clinical outcome and risk factors of those neonates suspected with sepsis admitted in Neonatal Intensive Care Unit of Tikur Anbessa Referral Hospital, Addis Ababa.

PART ONE: SOCIO-DEMOGRAPHY CHARACTERISTICS

Variables	Initial ----------		Date of admission---------
Sex	Male	Female	
Age (s) at admission	0-7	8-28	
Birth weight			
Address(residence) of family	Addis Ababa	Out of Addis Ababa	
Birth level of neonates			

PART TWO; CLINICAL CHARACTERISTICS

History of antenatal care	Yes	No		
Place of delivery	Hospital	Health center	Clinic	Home
Gestational Age	Pre term (<37wks	Term (37-42 wks.)	Post term (>42 wks.)	
Labor duration in hours	<18hr	>18hr		
Premature rupture of membranes	Yes	No		
UTI during pregnancy	Yes	No		
Discharge during pregnancy	Yes	No		
Febrile Hx of mother	Yes	No		
Hx of Chorioamnionitis	Yes	No		
Mood of delivery	Vaginal	CS		
Previous hospital admission of neonate	Yes	If yes		
	No			
Reason for current admission/admission diagnosis				

PART 3;DIAGNOSIS OF NEONATAL SEPSIS

Type of sepsis	Early onset	Late onset

Focus of sepsis infection: A) Urinary B) CNS C) GI D) Others……

E)unknown

Culture send	Yes
	No

If yes how many bottles ( )	Date of sample send (/ /)	Site of sample collection	Before Abs	After Abs
		A)Blood		
	Date of sample received (/ /)	B)Urine		
		C)CSF		
		D)Other		

Clinical variables	**Diagnostic test**
Have fever (T%.....)	**Culture and gram stain result**
Yes	Gram negative
No	Gram positive
Respiratory features (RR…..)	contaminant
Tachypnea	No growth
Apnea	**Appearance of CSF**
Hypoxia	Clear
Flaring or grunting	Cloudy
Irregular respiration	Bloody
Retraction	**Lumbar puncture result about**
No respiratory sign	WBC 0–5 cells/µL
More than one symptoms	>5 cells/µL
Gastro intestinal features	Glucose
Poor feeding	<40 mg/dL
Vomiting	> 40 mg/dL
Diarrhea	Protein
Abdominal distention	< 45 mg/dL
No symptoms	> 45 mg/dL
More than one symptom	Gram stain
Neurologic features	Gram negative
Decrease activity/lethargy	WBC result in CBC profile
Irritability	<4 billion cells/l
Tremors or seizure	5-10.5 billion cells/l
No neurologic signs	> 10.5 billion cells/L
Metabolic features (Glucose…	No CBC profile
Hypoglycemia	**CRP**>10 mg/l
No metabolic sign	

Organ function test	At admission	At last

PART THREE;TREATMENT RELATED CHARACTERISTICS

Antibiotic use	Drug (dose, frequency, route,,..)	Duration of treatment		If culture done		
		Start date	Stop date	Sen	Spe	Res
Ampicillin						
Gentamicin						
Cefotaxime						
Ceftriaxone						
Cefepime						
Cloxacillin						
Vancomycin						
Meropenum						
Ciprofloxacillin						
Other(						
Duration of antibiotic used						

Response of a patient after starting treatment

Time	A) Improving	B) no change	C)worsening
2nd days			
3rd -5th day			
6th-7th day			
8th-14th day			
15th -21th day			

For B and C Is there any change in treatment	No	If yes
	Yes	
Response after change		

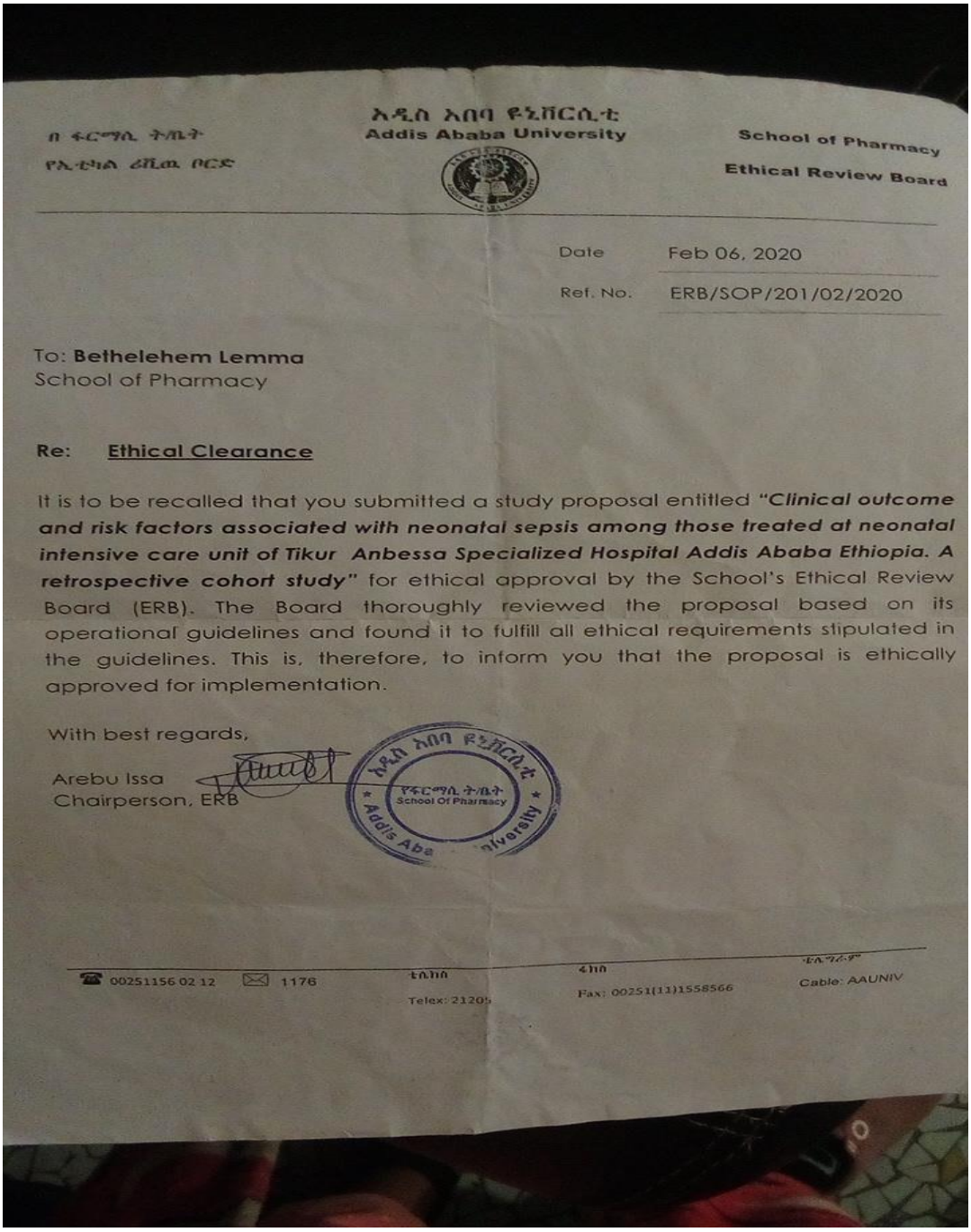
Length of hospital stay

PART FOUR ;CLINICAL OUTCOME

A)Discharged with improvement	B) Death

Name of investigator: _____sign_____Date_____

11.2. Annex II: Ethical clearance



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School of Pharmacy
Ethical Review Board

Date Feb 06, 2020

Ref. No. ERB/SOP/201/02/2020

To: **Bethelehem Lemma**
School of Pharmacy

Re: **Ethical Clearance**

It is to be recalled that you submitted a study proposal entitled ***"Clinical outcome and risk factors associated with neonatal sepsis among those treated at neonatal intensive care unit of Tikur Anbessa Specialized Hospital Addis Ababa Ethiopia. A retrospective cohort study"*** for ethical approval by the School's Ethical Review Board (ERB). The Board thoroughly reviewed the proposal based on its operational guidelines and found it to fulfill all ethical requirements stipulated in the guidelines. This is, therefore, to inform you that the proposal is ethically approved for implementation.

With best regards,

Arebu Issa
Chairperson, ERB

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