AUDIT OF ANTIBIOTIC PRESCRIBING PRACTICES FOR NEONATAL SEPSIS IN NEW BORN UNIT AT KENYATTA NATIONAL HOSPITAL

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STUDENT'S DECLARATION

I the undersigned, declare that this proposal is my original work. It has not been presented to any other university, college or institution for the purpose of academic credit.

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DEDICATION

To my beloved husband, Nikhil Pankhania, who has been my true inspiration, for his support and encouragement throughout. To my parents who were my first teachers and my family.

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ABBREVIATIONS

ETAT - emergency triage and treatment

KNH - Kenyatta National Hospital

NBU - new born unit

NICU - neonatal intensive care unit

WHO - world health organization

KDHS - Kenya demographic health survey

VLBW - very low birth weight

LBW - low birth weight

IV - intravenous

CRP - C reactive protein

CSF – cerebrospinal fluid

MDG – millennium development goals

CPAP – continuous positive airway pressure

EONNS – early onset neonatal sepsis

LONNS – late onset neonatal sepsis

GBS – group B Streptococcus

DEFINITION OF TERMS

1. Neonate: An individual of age between 0 days to 28 days.

2. Neonatal Sepsis: Clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteraemia in a neonate.

3. Early onset neonatal sepsis: is a clinical syndrome of bacteraemia with systemic signs and symptoms of infection in the first 72 hours of life.

4. Late onset neonatal sepsis: is defined as infection occurring at more than 72 hours of age after birth.

5. Proven Sepsis: A positive blood, CSF or urine culture in the presence of clinical signs and symptoms of infection.

6. Probable Sepsis: Presence of signs and symptoms of infection and at least two abnormal haematological findings when blood culture is negative.

7. Possible Sepsis: Presence of clinical signs and symptoms of infection plus raised CRP level when blood culture is negative.

8. Clinical audit: The systematic and critical analysis of the quality of clinical care.

9. Empirical antibiotic therapy: The early and appropriate initiation of antimicrobial agents in high-risk neonates before the result of blood culture susceptibility is defined as "empirical antibiotic therapy."

10. Term new-born: baby born after 37 completed weeks of gestation.

11. Low birth weight: refers to infants weighing less than 2,500 grams at birth.

12. Very low birth weight: refers to infants weighing less than 1,500 grams at birth.

13. Prematurity: Neonate delivered before 37 weeks gestation.

14. At-risk new-borns: are those who have perinatal risk factors (see Table 2) or those with 1 or more clinical feature suggestive of sepsis (see Table 3).

15. Tachypnoea: is a respiratory rate ≥ 60 breaths/minute.

16. Apnoea: Cessation of breathing for more than 20 seconds accompanied by bradycardia.

17. Birth asphyxia: is defined by WHO as failure to initiate sustained breathing at birth plus an Apgar score less than 7 at 5 minutes.

18. Antimicrobial resistance: is defined by WHO as resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it.

ABSTRACT

BACKGROUND

Neonatal sepsis is a major contributor of morbidity and mortality globally. Neonates usually present with nonspecific signs, hence requires a high index of suspicion(1). Neonates with sepsis deteriorate rapidly, leading to death, if treatment is delayed. The Ministry of Health, Kenya has published guidelines for management of neonatal sepsis in Basic Paediatric Protocols (revised in 2016), which are widely used(2). Auditing of antibiotic use is necessary as antibiotic misuse is one of the most important factor for development of antibiotic resistance (3,4).

At the Kenyatta National hospital, a large national tertiary referral hospital, average 250 neonates per month are being admitted in NBU. Since the guidelines on management of neonatal sepsis were made in Kenya, antibiotic use has not been audited in NBU at KNH. Documentation of antibiotic prescribing practices will improve our knowledge, inform our ways of practices, help correct errors and allow staff training to prevent misuse and antibiotic resistance.

OBJECTIVES

To assess the antibiotic prescribing practices against recommended Kenyan guidelines(2) for neonatal sepsis among neonates admitted to NBU at KNH. In addition, the study described the outcome of neonates with neonatal sepsis on antibiotics within 7 days.

METHODS

This was a prospective audit carried out over period of three months in NBU at KNH. Informed consent was obtained from each participant enrolled in the study. Files (admission record) of neonates who met the inclusion criteria were audited after review by the doctor on call at admission. Information regarding patient's demographic data, maternal and neonatal history (risk factors),clinical signs examined, laboratory investigations requested, diagnosis, antibiotics prescribed (choice, dosages, frequency and duration) was abstracted from files using a structured questionnaire. Review of the files was done daily for 5 days to check whether antibiotics were continued, stopped or changed to second line based on clinical condition of the neonate. Data on outcome of the neonate with neonatal sepsis were determined within 7 days or on discharge (survived/died).

RESULTS

Overall documentation of perinatal risk factors and clinical features present was very poor. The most commonly documented perinatal risk factors were low birth weight in 100%, prolonged rupture of membranes 51.6%, foul smelling liquor in 11.2%, chorioamnionitis in 10.2% and difficult or

prolonged labour in 7.8%. Overall 53(16.6%) neonates had maternal risk factors present. The clinical features not documented by clinician on admission were convulsions in 252(41.05%), grunting in 128(20.85%), lower chest wall indrawing in 76(12.4%) and lethargy in 65(10.6%). The rate of investigations to confirm infection was very low. Blood cultures were done only in 13(4%) neonates on admission, while complete blood count and C reactive protein were done in 224(70%) and 198(62%) respectively. Immature to total lymphocyte count and lumbar puncture were not done in any of the neonates. Appropriate antibiotics as per the Kenyan guidelines were prescribed in 313(97.8%) of neonates on admission. Appropriate doses of penicillin and gentamicin were given in 310(96.9%) and 282(88%) respectively on admission. There was prolonged unnecessary use of antibiotics in neonates who improved clinically at 48 – 72 hours. Neonates who improved clinically at 48 hours were 148(53.62%), yet antibiotics were stopped in 8(2.9%) only. At 72 hours 168(65.12%) neonates improved clinically, but antibiotics were stopped only in 22(8.53%).

Overall mortality among 320 neonates admitted was 80(25%) over 7 days. Mortality among preterm neonates (< 37 weeks gestation) was 70(21.8%). Twenty (25%) neonates died within the first 24 hours, 24 (30%) died within 24 - 48 hours, and 36 (45%) died between 48 hours - 7 days. Out of the neonates who died within 48 hours, 38(11.8%) were preterm.

CONCLUSION

There was poor documentation of clinical features, perinatal risk factors and condition of the neonates at the time of change of antibiotics. Appropriate antibiotics as per the Kenyan guidelines (Basic Pediatrics Protocols-2016) were given in 97.8% of neonates on admission. The rate of investigations to confirm infection was very low. Blood cultures were done only in 4% of neonates on admission and lumbar punctures were not done.The continuation of antibiotics was inappropriate. Overall mortality was high in neonates at 25% (80). Mortality among preterm neonates (< 37 weeks gestation) was 70(21.8%). Forty four (55%) died within 48 hours.

RECOMMENDATIONS

Proper documentation of perinatal risk factors and clinical features is advocated. Full septic screen should be done on admission to confirm infection and while changing antibiotics. We should emphasize on discontinuing empiric antibiotics as soon as the neonate is clinically stable and laboratory tests done are normal. Antibiotic stewardship should be promoted.

CHAPTER 1: INTRODUCTION

BACKGROUND

According to Global Health Observatory data, 2.6 million neonates died in 2016. Among children under-5, neonatal deaths account for 46% annually, with neonatal mortality rate of 19 per 1000 live births. Seventy five percent of all neonatal mortality occurs within the first seven days, and around 25 - 45% within the first 24hours.Mortality causes are demonstrated in figure 1 below. Sepsis accounts for around one third deaths in neonates worldwide(5).

Figure 1: Causes of mortality among children under 5 years

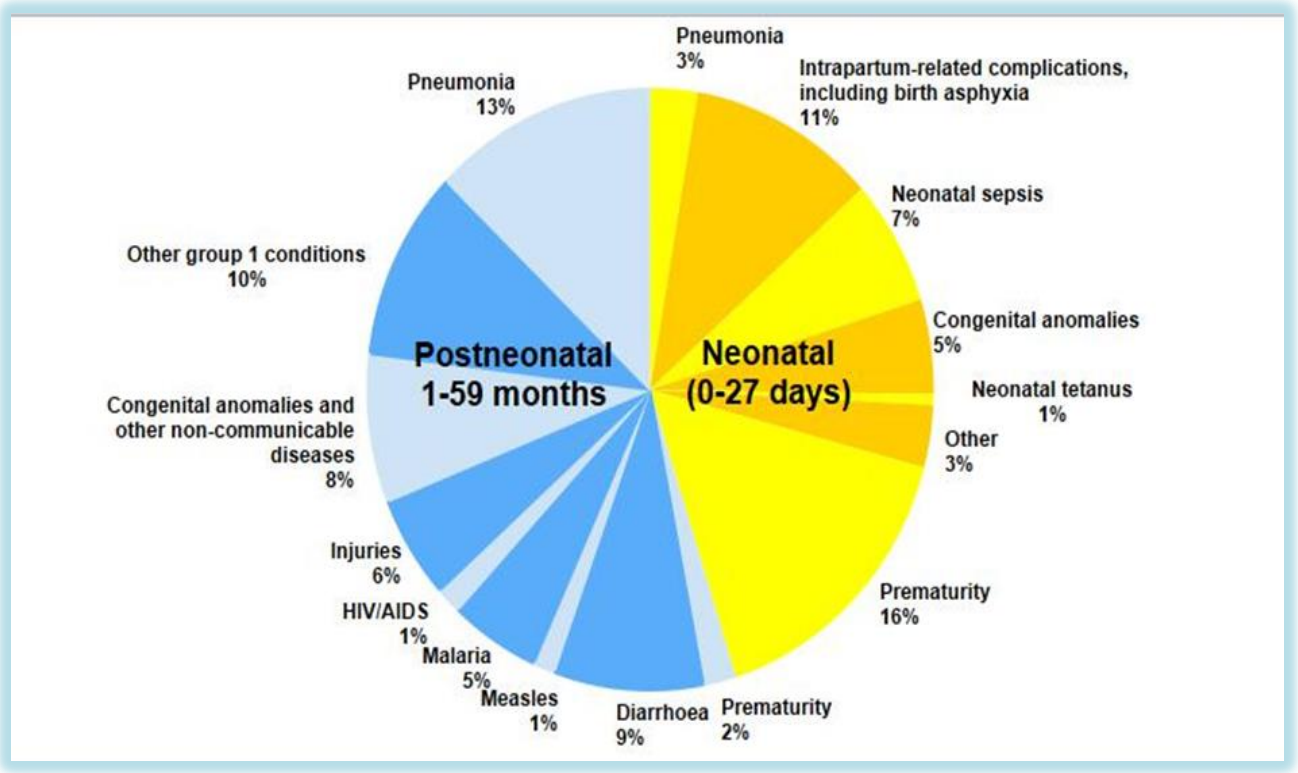
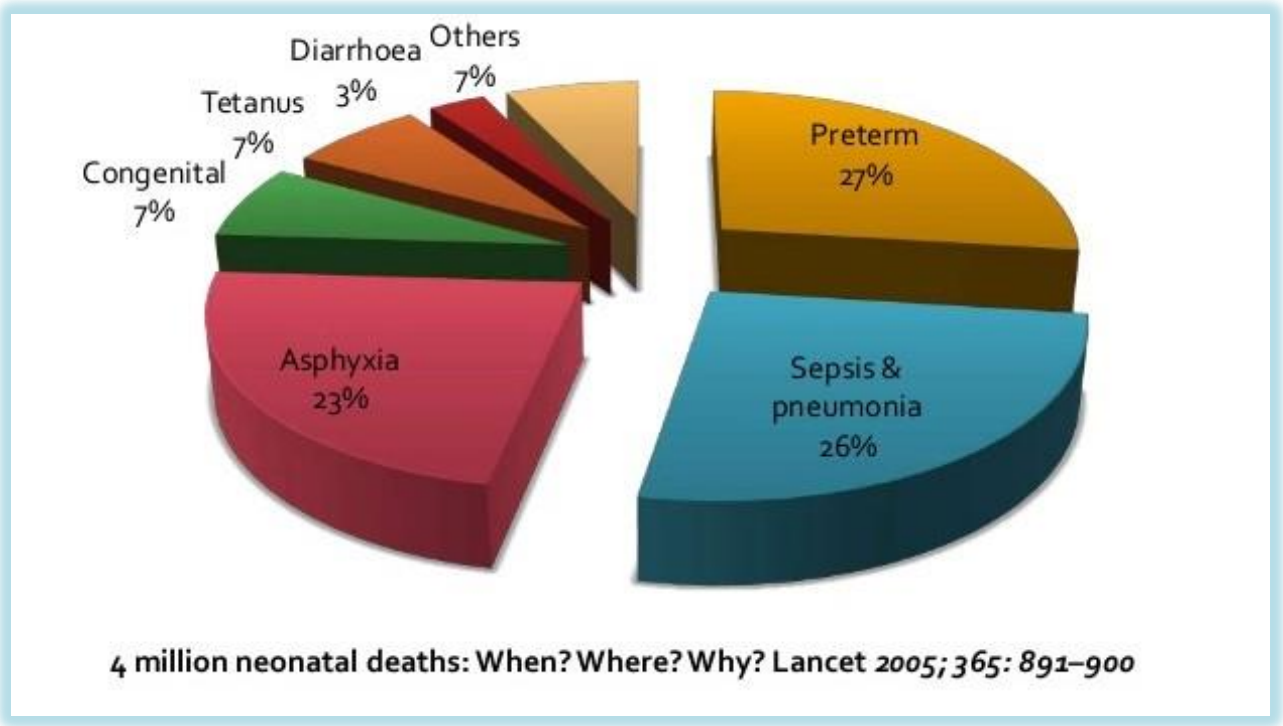


Figure 2: Causes of neonatal mortality



Neonatal mortality has minimally declined despite gains in child survival following implementation of the MDG's. The current neonatal mortality rate is 19 deaths per 1000 live births (2016) and has reduced from 37 deaths per 1,000 live births (1990) worldwide. This decline has been slower than the infant mortality rate. From 1990 to 2016 neonatal mortality has reduced by 49%, while the infant mortality rate reduced by 62%(6,7).

Figure 3: Target for MDG - 4

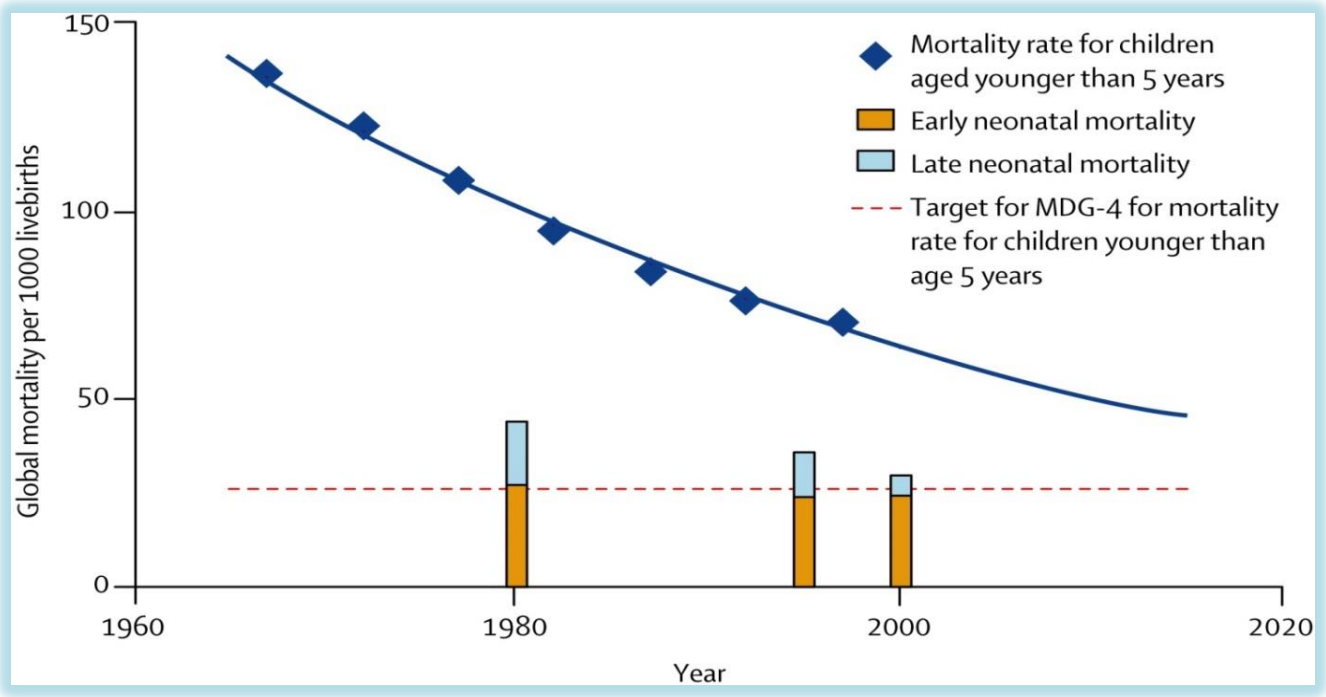
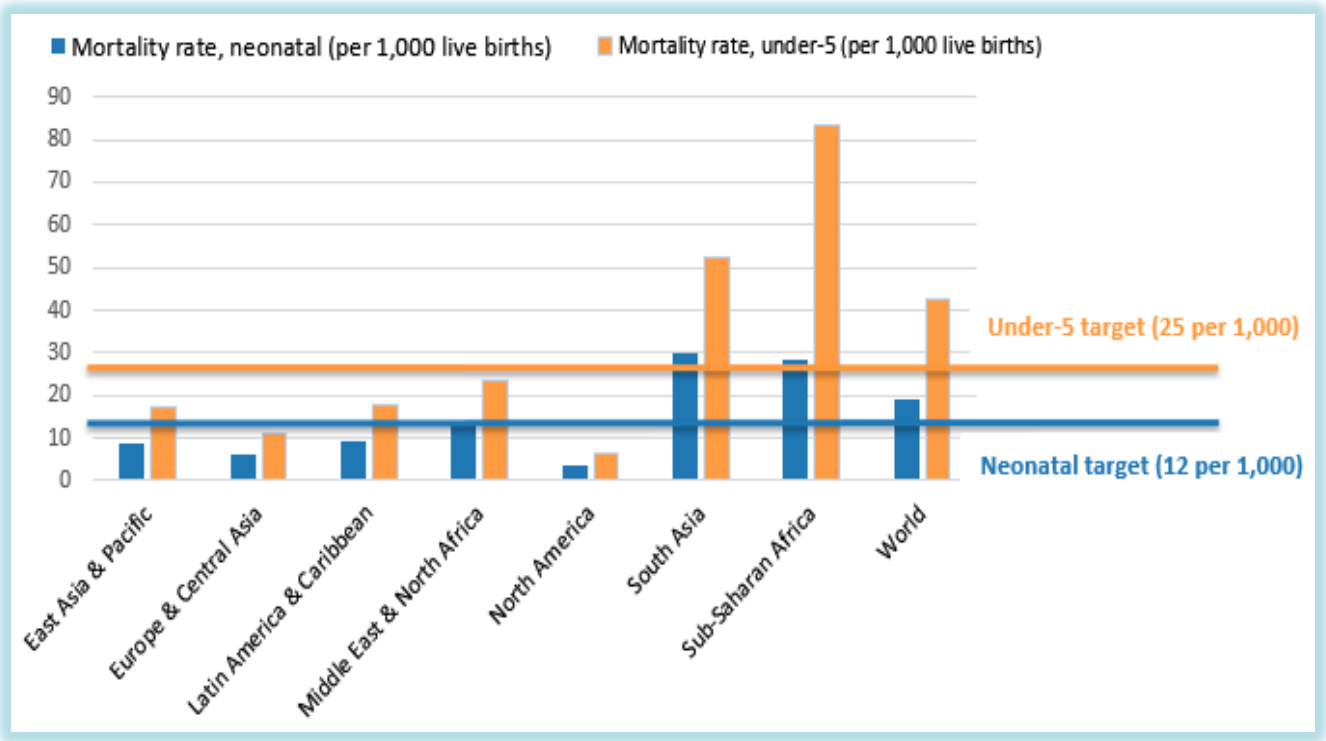
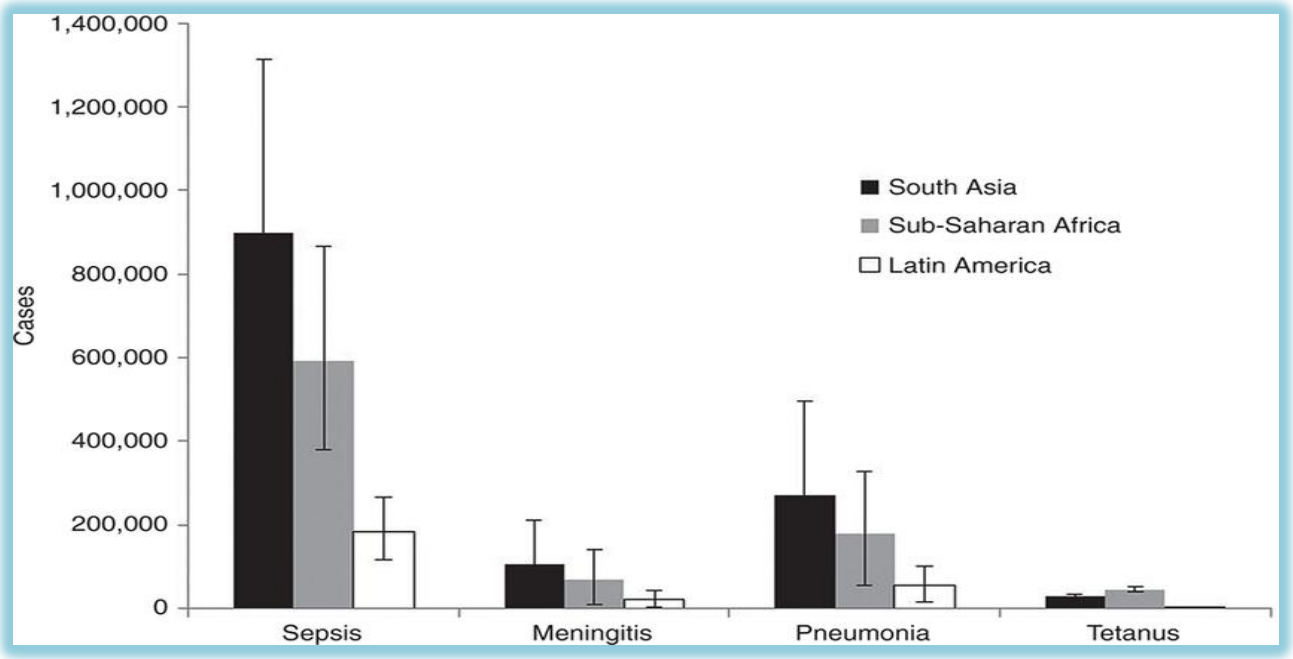


Figure 4: Under - 5 and neonatal mortality rates



World over, neonatal sepsis is a major contributor to neonatal morbidity and mortality. The highest burden of disease is in developing countries like Sub Saharan Africa and South Asia (7). According to KDHS – 2014, the neonatal mortality rate in Kenya has decreased from 31 in 2008-09 to 22 deaths per 1000 live births in 2014(8).

Figure 5: High burden of disease in South Asia and Sub - Saharan Africa

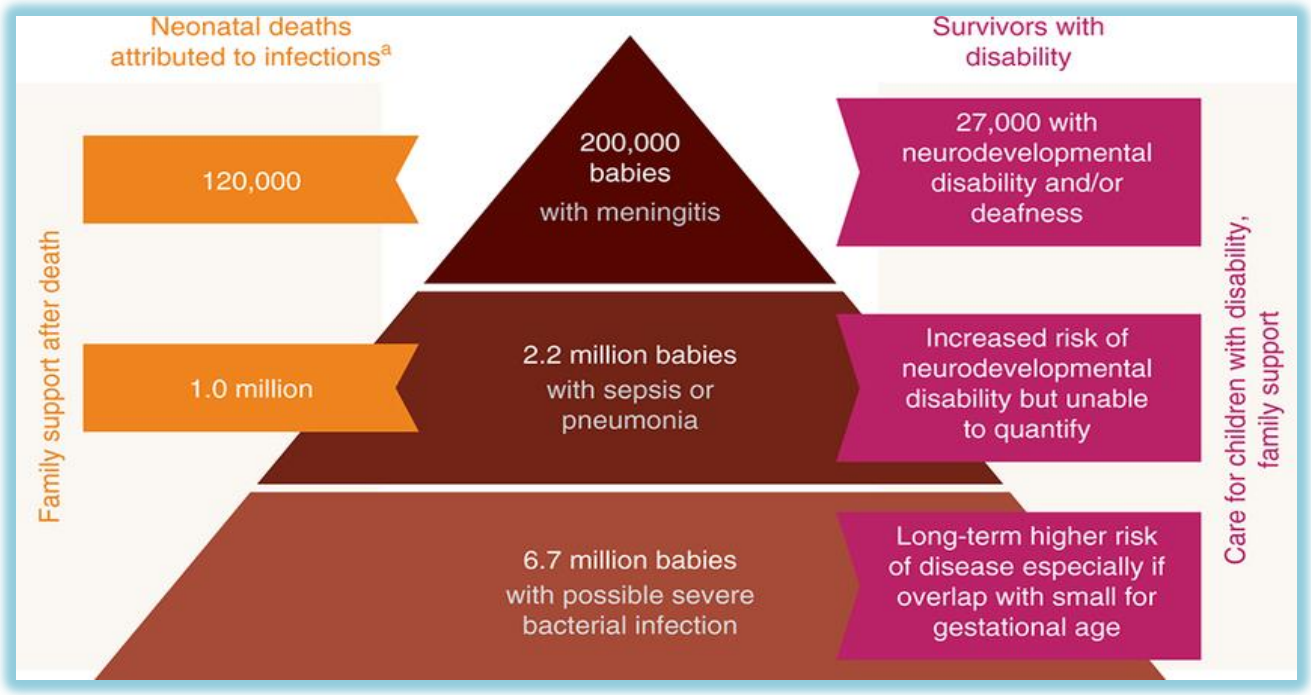


Neonatal sepsis is a clinical condition identifiable by generalized signs of infection with bacteraemia in the first 28 days of life. Early onset neonatal sepsis (EONNS) is defined as infection with onset of symptoms and signs within first 3 days of birth, whereas, late onset sepsis (LONNS) is defined as infection with onset of signs and symptoms occurring after 72 hours of birth.

Neonatal sepsis usually has non-specific presentation. Grave consequences including neurodevelopmental deficits and or death can occur if there is delay in initiation of effective antibiotics(9). Therefore, clinicians are urged to start empirical antibiotics to the neonates who are symptomatic or at high risk of sepsis while waiting for results of blood culture(1). Antibiotics are the most frequently prescribed medicines in NBU. Antibiotics should be used judiciously either as prophylaxis for neonates at risk or as empiric therapy in neonates presenting with features of sepsis. Appropriate antibiotic therapy for neonatal sepsis and meningitis has shown to reduce neonatal deaths and long term complications such as cerebral palsy(10,11). There is paucity of data on rational use of antibiotics in neonates.

Neonatal sepsis is associated with high morbidity, neurodevelopmental impairment is increasingly been seen in survivors(12,13). Systematic reviews and meta-analyses done in Third world countries estimated moderate to severe neurodevelopmental impairment after neonatal meningitis in 23% of survivors(12) including cerebral palsy, lower intelligence quotient and psychomotor development index scores, visual deficit and growth failure on follow up(14,15).

Figure 6: Summary of morbidity and mortality outcomes of neonates born in South Asia, sub-Saharan Africa, and Latin America in 2010.



ANTIMICROBIAL RESISTANCE

Emergence of multidrug-resistant organisms including super-bugs is a major issue worldwide. Judicious use of antibiotics can be life-saving; however, anti-microbial resistance can develop by use of broad-spectrum antibiotics and prolonged treatment with empirical antibiotics(3,16). These antibiotics alter the natural micro-environ of the gut, resulting in development of antibiotic resistance among normal flora organisms or the appearance of other pathogens. The most common cause of neonatal sepsis worldwide is Staphylococcus Aureus. Methicillin resistant Staph Aureus (MRSA) is a major contributor to hospital acquired infections that causes severe morbidity and mortality. In America and Europe, MRSA strains account for 29–35% of all isolates in hospitals(17,18). Antimicrobial resistance could be the reason for failure in achieving our target for MDG – 4. Antibiotic prescribing practices should be evaluated periodically for its rational use to prevent emergence of resistance(3). There is narrow pipeline for new antibiotics.

ADVERSE EFFECTS WITH PROLONGED ANTIBIOTIC USE

Neonates are at increased risk to contract infections(9) and are also prone to adverse effects of drugs due to differences in pharmacodynamics and pharmacokinetic characteristics(19). Invasive candidiasis has been on the rise due to altered gut colonization by use of broad-spectrum antibiotics like third generation cephalosporin (20). Prolonged duration of antibiotics is usually associated with adverse

outcomes like necrotising enterocolitis, sepsis occurring after 3 days and death(20). Some neonatal infections can also occur due to viruses or fungi and must be distinguished from bacterial sepsis(1).

In an effort to reduce neonatal mortality rate, Ministry of Health Kenya, published Basic Paediatric Protocols(February-2016), which has guidelines for management of neonatal sepsis(2). Training of health personnel on the Kenyan guidelines is done by ETAT+. Adherence to guidelines in terms of choice and duration of antibiotics is vital in order to reduce spread of resistance in the hospital, as well as in the community(3,4). Rational use of antibiotic is recommended.

CHAPTER 2: LITERATURE REVIEW

2.1 EPIDEMIOLOGY

Based on systematic review, incidence of neonatal sepsis varies from 1.5 to 3.5 per 1000 for EONNS and twice as much(6 per 1000 live births) for LONNS in the United States and Australasia, whereas, it ranges from 3.5 to 8.9 per 1000 live births in South America and the Caribbean, highest in Asia (7.1 to 38 per 1000 live births), from 6.5 to 23 per 1000 live births in Africa(21).

In year 2005-2008 in United States, Active Bacterial Core surveillance found that the incidence of neonatal sepsis was 0.77 per 1000 live births in 2005 and 0.76 per 1000 live births in 2008. The estimated burden of early onset sepsis was approximately 3320 cases, including 390 deaths annually(22). A descriptive prospective study done by Saini et al in 2016 in India neonatal sepsis was second leading cause of neonatal morbidity(3.99%)(23). Sarasam et al in India showed incidence of culture positive sepsis of 21.5%, of these 54% was early onset sepsis (15).

Seale et al in a review article, described that the highest burden of disease is in Sub Saharan Africa(24). Gebremedhin et al in Ethiopia, showed prevalence of early onset sepsis at 76.8%(25). In Tanzania, Jabiri et al showed prevalence of 31.4% for neonatal sepsis(26). A prospective study done in Egypt showed the incidence of suspected neonatal sepsis of 45.9%, in which 44.2% had EONNS, while 55.8% had LONNS. The mortality rate was 51% for proven early onset sepsis and 42.9% for proven late onset sepsis(27).

In Kenya, Kumar et al showed that out of 310 neonates, 83 had proven sepsis and 94 had probable sepsis(28). According to retrospective study done by Geyt et al, from 2011 to 2014, in a county referral hospital in central Kenya, 23.9% had a diagnosis of neonatal sepsis at admission; mortality due to sepsis was 18.2%(29). A study done by Ng'ang'a et al, in post natal wards of KNH, showed prevalence of 12% for proven (blood culture positive) sepsis and 58% for probable sepsis ($\geq$ 1 clinical feature of sepsis or a positive CRP) in term neonates(30). A cross-sectional study done by Muturi et al at Kisii Level 5 Hospital, showed prevalence of clinical sepsis at 19.7%(31).

A study done by Musoke et al in 1992 at KNH NBU, showed overall neonatal mortality of 24.6%(32). A retrospective study done by Simiyu et al in 2000 at KNH showed overall neonatal mortality of 57.4% with incidence of suspected sepsis of 37%(33).

Table 1: Summary of various studies

Author/setting	Sample size	Incidence/prevalence	Mortality
Weston et al/ United States(22)	159,000 live births in 2005 and 233,000 live births from 2006–2008	0.77cases/1,000 live births in 2005 and 0.76 cases/1,000 live births in 2008	390 deaths annually
Saini et al/India(23)	6509 live births	3.99%	14.9%
Sarasam et al/India(34)	5202	21.5% had culture positive sepsis with 54% was early onset sepsis and 46% late onset sepsis	353
Gebremedhin et al/ Ethiopia(25)	234	76.8% had early onset sepsis	
Jabiri et al/Tanzania(26)	220	31.4% had sepsis	
Shehab El-Din et al/Egypt(27)	344	45.9% had suspected sepsis with 44.2% EONNS and 55.8% LONNS	51% for EONNS and 42.9% for LONNS
Kumar et al/Kenya(28)	310	83 had proven sepsis and 94 had probable sepsis	
Geyt et al/Kenya(29)	1262	23.9% had diagnosis of neonatal sepsis	overall mortality was 24.7%, 18.2% was attributed to sepsis
Ng'ang'a et al/Kenya (30)	139	12% had proven sepsis and 58% had probable sepsis	2% of whom had probable sepsis
Muturi et al at/ Kenya(31)	80	19.7% had clinical sepsis	27.2%
Simiyu et al/Kenya(33)	533	37% suspected sepsis	57.4%

2.2 ETIOLOGY AND RISK FACTORS

Neonatal sepsis is mainly caused by bacterial pathogens.

Early onset sepsis is usually acquired during intrapartum period(35). The major determinant conditions for EONNS are prolonged rupture of membranes, chorioamnionitis, prematurity, maternal fever during labour and delivery and insufficient intrapartum antibiotic prophylaxis(35–37). Any form of intrapartum antibiotic given during labour and delivery is associated with decreased risk(37). Neonatal factors are low birth weight (<2500 grams), prematurity (<37 weeks gestation) and twin or sibling treated for sepsis(36).

The common causative organisms for EONNS are GBS(43-58%), Escherichia coli(18-29%), Staphylococcus Aureus(2-7%), Coagulase negative Staphylococcus(1-5%), Listeria Monocytogenes(0.5-6%) and other gram-negative bacteria(7-8%), GBS being the most common(18,22). In VLBW new-borns, Escherichia Coli infections are more common than GBS (18).

Late onset sepsis is mostly acquired postnatally, usually caused by hospital acquired infections. Preterm neonates are more prone to LONNS because of poor immunity, hospitalizations for longer duration, endotracheal intubation and mechanical ventilation for longer duration, use of central venous catheters, parenteral feeding, use of indwelling catheters, and other invasive procedures(36,38).

The common causative organisms for LONNS are Coagulase negative Staphylococcus (39-54%), Escherichia coli (5-13%), Klebsiella sp. (4-9%) and Candida sp. (6-8%). Staphylococcus Aureus(6-18%), Enterococcus sp.(6-8%) and Pseudomonas Aeruginosa(3-5%) are other less common causes of LONNS(28, 29).

In Kenya, the study done by Ng'ang'a et al, on prevalence and aetiology of EONNS in term neonates who were at risk in post natal wards at KNH in 2013, concluded that Coagulase negative Staphylococcus accounted for 43.5% of isolates, while, Gram negative bacteria, Escherichia coli, Enterobacter spp. and Proteus spp. accounted for 21% of isolates(30). Maore et al in 2015 at Pumwani Maternity Hospital showed the prevalence of confirmed bacterial sepsis 32% (48/150). In his study, Gram positive bacteria like Staphylococcus Aureus and Streptococcus viridian accounted for 70% of the total isolates and gram negative bacteria like Escherichia coli and Klebsiella species accounted for 18% of the total isolates. Staphylococcus Aureus was the most common pathogen in EONNS while Staphylococcus Aureus and Streptococci pneumonia accounted for LONNS(40). In a study done by Kumar et al in 2006 in NBU at KNH, most frequently isolated organisms were Enterobacter Agglomerans in EONNS (27.6%). Enterobacter Agglomerans, Citrobacter and Acinetobacter species were among the common organisms in LONNS. Overall 71.6% were gram negative organisms, 22.4% were gram positive organisms, with Candida being found in 4.6%(28).

Table 2: Causative organisms and risk factors associated with neonatal sepsis

Neonatal sepsis	Causative organisms	Risk factors
EONNS	• GBS • Escherichia coli • Streptococcus viridian • Enterococci • Staphylococcus Aureus • Pseudomonas Aeruginosa • Other gram-negative bacilli	• Maternal GBS colonization • Chorioamnionitis • Premature rupture of membranes • Prolonged rupture of membranes (>18h) • Prematurity (< 37 weeks) • Multiple gestation
LONNS	•Coagulase-negative Staphylococci • Staphylococcus Aureus • Candida Albicans • Escherichia coli • Klebsiella Pneumoniae • Enterococci • Pseudomonas Aeruginosa • GBS	• Prematurity • Low birth weight •Use of indwelling catheter for longer duration • Invasive procedures • Pneumonia associated with ventilator • Use of antibiotics for prolonged period

2.3 DIAGNOSIS

It is always challenging for clinicians to make early diagnosis of neonatal sepsis because of its subtle and non-specific presentation and multiple other conditions resemble it. Clinicians require high index of suspicion based on risk factors and physical examination. The criteria to make diagnosis of neonatal sepsis include clinical presentation, positive blood cultures and non-specific laboratory tests.

2.3.1 Clinical Diagnosis

The common cause of respiratory distress in preterm neonates is usually surfactant deficiency or retained lung fluid. Any respiratory distress within first 24 hours of life should be treated with antibiotics because sepsis may be contributing or may be the primary cause, even if there are no known risk factors(41).

According to several studies done, the following are maternal and neonatal risk factors for EONNS (36,37)(see Table 3).

Table 3: Perinatal risk factors(2)
Maternal fever during labour and delivery ≥38ºC (100.4º)
Prolonged rupture of membranes (> 18 hours)
Foul smelling liquor
Chorioamnionitis
Maternal Group B Streptococcus colonization
Low birth weight (< 2500g)
Intrapartum maternal sepsis

Any form of intrapartum antibiotic given during labour and delivery is associated with decreased risk of neonatal sepsis (20). Neonatal factors include prematurity, low birth weight (LBW) and an affected twin or sibling (36).

According to several studies done, the following are clinical features suggestive of sepsis(42,43) (see Table 4).

Table 4: Clinical features suggestive of early onset sepsis
Refusal to breastfeed or feeding intolerance
Lethargy or change in level of activity
Convulsions
Bulging fontanel
Hypothermia or hyperthermia
Apnoea
Features of respiratory distress(severe chest wall indrawing, tachypnoea or fast breathing, grunting, cyanosis or decreased oxygen saturation)
Jaundice within 24hrs of birth
Pallor
Septic spots on the skin or septic umbilicus

Adopted from Basic Paediatric Protocols - February 2016(2)

2.3.2 Laboratory Diagnosis

The benchmark of diagnosis of neonatal sepsis is isolation of bacteria from blood, CSF or urine(44). Total leucocyte count, C-reactive protein, absolute neutrophil count, micro-erythrocyte sedimentation rate, immature to total neutrophil ratio, Procalcitonin and cerebrospinal fluid analysis are various components of the septic screen(44,45).

Blood culture

Blood culture remained the gold standard; however, several factors like blood volume infused, maternal antibiotic exposure, level of bacteraemia and laboratory capabilities affects its positivity rate(11). There is a significant time lag before blood culture results are available; as a result, empiric antibiotic therapy is initiated on basis of clinical assessment and laboratory tests while awaiting blood culture results. Musoke et al in NBU of KNH reported overall 16.7% of positive blood cultures. The Gram negative isolates were 73.6% with Klebsiella species at 31%(3). Kumar et al at KNH isolated organisms from 83 blood cultures and 2 CSF cultures. The Gram negative organisms were 71.6%, Gram positive organisms were 22.4%, whereas, Candida was found in 4.6%(28). A study done by Ahamed et al at Pumwani Maternity Hospital reported positive blood cultures rates of 20.8%(47). Blood culture may be false-negative in a symptomatic baby, if mother was given antibiotics prenatally or if the blood sample was collected with improper technique.

Culture of urine, gastric contents, and body surfaces is not a part of neonatal septic screening(10). Urine culture had a significantly lower yield in diagnosing neonatal sepsis(48).

Haematological parameters

In the diagnosis of neonatal sepsis total blood cell counts have less importance. Leucopenia, absolute neutropenia and high immature/total ratio were associated with early-onset sepsis with low sensitivities (0.3%-54.5%)(49). Leucopenia/leucocytosis, absolute neutrophilia, high immature-to-total neutrophil ratios and thrombocytopenia were associated with late-onset sepsis(50). According to Manroe et al neutropenia is a better marker with better specificity for neonatal sepsis than neutrophilia. There are other few conditions that can cause neutropenia like maternal pre-eclampsia/eclampsia, perinatal asphyxia, and hemolytic disease(51). According to Rodwell's hematologic scoring system**,** the likelihood of neonatal sepsis is high with higher score(52). According to study done by Narasimha et al, the most sensitive tests for diagnosing neonatal sepsis were I:T PMN ratio and degenerative changes. High sensitivity was noted for abnormal immature to mature PMN ratio in identifying sepsis(53).

Figure 7: Rodwell's hematologic scoring system(52)

Criteria	Abnormality	Score
I:T>0.2	Increase	1
Total PMN count	Increase/decrease	1
I:M	≥0.3	1
Immature PMN count	Increase	1
Total WBC count	Increase/decrease (≥5,000/mm3 or 25,000, 30,000, and 21,000/mm^3 at birth, 12-24 h and day 2 onwards, respectively	1
Degenerative changes in PMN	≥0.3+	1
Platelet count	≤1,00,000/mm^3	1
Score	Interpretation	
≤2	Sepsis is very unlikely	
3/4	Sepsis is suspected	
≥5	Sepsis is very likely	

I:T=Abnormal immature to total neutrophil ratio; I:M=abnormal immature to mature neutrophil ratio; PMN=polymorphonuclear, WBC=white blood cell

CRP

It is an acute phase reactant which increases in inflammatory conditions, including sepsis. Serial CRP levels during the first 12-24 hours of presentation may be useful for the early identification of neonates in whom antibiotics can be safely discontinued(54,55). Kumar et al in 2006 at KNH found the CRP to have a sensitivity of 88.9% and a specificity of 82.5% for EONNS, and a sensitivity of 98.2% and a specificity of 86.2% for LONNS(28). CRP can be used to follow the response progress of treatment, if CRP remains persistently high during antibiotic therapy; there might be possibility of fungal or viral infection, antibiotic resistant organisms and or development of a complication(56). There are some other non- infectious conditions like meconium aspiration syndrome , hypoxic perinatal asphyxia and tissue injury (bruises, cephalhematoma) where CRP levels can be high(57).

Procalcitonin

It is a precursor protein of calcitonin with no hormonal activity, tissue discharge of procalcitonin raises with infection making it a potential marker for early detection of sepsis. A meta-analysis showed overall sensitivity of 81% and specificity of 79%(58). Procalcitonin is a better predictive marker for neonatal sepsis within the first 12 hours of life than CRP, however, it has low specificity than CRP(59).

CSF Analysis

It is still controversial whether a lumbar puncture is necessary in a neonate with suspected early-onset sepsis(60). It must be performed when there is high index of suspicion for meningitis (i.e. change in level of activity, bulging fontanelle or history of convulsions). A retrospective study done by Johnson

et al concluded that lumbar puncture is unnecessary in asymptomatic full-term neonates(61). Stoll et al reported that meningitis may be underdiagnosed among VLBW neonates. He concluded that among VLBW neonates with meningitis one third(45 of 134) had negative blood cultures(62). Laving et al in NBU of KNH reported prevalence of meningitis at 17.9% amongst cases of suspected sepsis. Among those with meningitis, 53.3% had confirmatory blood cultures(63). Every symptomatic neonate, must have a lumbar puncture done as an initial evaluation to exclude meningitis since the diagnosis of meningitis alters the length of antibiotic treatment and prognosis.

Chest Radiograph

It should be done in any neonate presents with signs of respiratory distress or apnoea to rule out other conditions such as meconium aspiration syndrome, respiratory distress syndrome, congenital diaphragmatic hernia, and congenital heart diseases.

2.4 MANAGEMENT

INTRAPARTUM ANTIBIOTIC PROPHYLAXIS TO PREVENT EARLY-ONSET GBS INFECTION

The most common cause of EONNS is GBS and is a major contributor of neonatal mortality and morbidity(33). In developed countries, routine screening for vaginal and rectal GBS colonization is done between 35 and 37 weeks gestation for all pregnant mothers. The incidence of early-onset GBS infection has been decreased with maternal intrapartum intravenous antibiotics use(64). A South African study showed prevalence of GBS for EONNS and LONNS at 49.2% and 75.7% respectively(65). Mohamed et al at KNH reported the prevalence of GBS colonization at 25.2% among antenatal mothers(66).

Indications of Intrapartum GBS prophylaxis (*Adopted from Prevention of Perinatal Group B Streptococcal Disease, Revised Guidelines from CDC, 2010)* (64)

- Virulent GBS disease in previous infant
- Positive GBS urine culture anytime during the current pregnancy
- Current pregnancy with a positive GBS vaginal-rectal screening culture in late trimester
- GBS status not known(culture not done, incomplete, or results not known) at the onset of labour and any of the following:
    - Delivery before 37 weeks of gestation
    - Rupture of membranes for ≥18 hours
    - Maternal fever (Temperature ≥38.0°C)
    - Intrapartum PCR positive for GBS

SUPPORTIVE

Neonates with sepsis require proper supportive care. Hypo/hyperthermia should be avoided; the neonate should be nursed in a thermo-neutral environment. Oxygen saturation should be maintained within normal range; if necessary respiratory support is indicated. The neonate should be monitored for hypo/hyperglycaemia. If the neonate is not stable hemodynamically, intravenous fluids should be administered. Crystalloids/colloids and inotropes should be used to maintain normal tissue perfusion and blood pressure. In case of anaemia or bleeding diathesis packed red cells and fresh frozen plasma should be administered(67).

DEFINITIVE

Prophylaxis:

- As recommended by the Kenyan guidelines(Basic Paediatric Protocols - Feb 2016), Benzyl Penicillin and Gentamicin prophylaxis be initiated to all neonates with any one of the risk factors as mentioned in Table 3 soon after birth.
- Septic screen (Full hemogram, CRP, I:T ratio, blood culture, lumbar puncture) should be done as soon as possible, while continuing antibiotics.
- At least 4 doses of Penicillin + 2 doses of gentamicin should be given for 48 – 72 hours. (See Appendix 12.5 for management of neonatal sepsis according to Kenyan guidelines)
- and may be stopped at 48-72 hours
    - if the neonate has remained clinically stable and breast feeding well, or
    - blood culture is negative, and
    - weak clinical suspicion of infection, and
    - the levels and trends of CRP are convincing.
- When results of cultures and susceptibility are available and if the patient does not respond clinically, the choice of antibiotics should be re-evaluated.

According to Kenyan Guidelines (2),

- The recommended duration of antibiotics is 48 hours for any neonate with signs of infection and it can be stopped after 48 hours if signs of possible infection have resolved and the neonate is breastfeeding well.
- Antibiotics should be given for 72 hours for any neonate who has skin infection with signs of generalised illness and it can be stopped after 72 hours if the neonate is breastfeeding well, has no fever or any other issue.

- For clinical or radiological pneumonia antibiotics should be given for a minimum of 5 days or until the neonate clinically stable for 24 hours.
- The antibiotics should be continued for 7 days or until completely well for severe neonatal sepsis.
- For neonatal meningitis a course of antibiotics for 14 days is usually recommended however treatment for up to 21 days may be required for Gram negative infections.

2.5 ANTIBIOTIC PRESCRIBING PRACTICES

Appropriate/inappropriate use of antibiotics

A study done by Cantey et al in 2011-12 in Texas concluded that 94% of antibiotic use was empirical, and only 5% of antibiotic use was for confirmed sepsis. When cultures were sterile, antibiotics were stopped only in 63% at 48 hours and 26% received antibiotics for ≥120 hours despite negative cultures. Prolonged antibiotic therapy ≥7 days was given for pneumonia and culture-negative sepsis in 64% and 69% of cases, respectively(68). According to review article in United Kingdom in 2012, an audit on antibiotic treatment for suspected early onset neonatal sepsis, all 22 neonates(screened by NICE-2012 criteria) received antibiotics for >48 hours, despite negative haematological parameters (CRP, full blood count) and blood culture. Three (14%) were treated for presumed early-onset sepsis, yet they did not match the NICE screening criteria; before starting antibiotics these babies could have been observed for 24 hours(69).

A retrospective study done by Kithinji et al in 2011 at KNH concluded that the first line antibiotics were given to 64.4% of neonates, out of them 37.5% were having error in dose(70). Simiyu et al in the NBU of KNH concluded that 86% of neonates had antibiotics started yet only 37% had a diagnosis of suspected sepsis. In only 13.5% of cases was change of antibiotics was guided by culture and sensitivity reports. Blood cultures were done only in 14%(71). An audit done by Aluvaala et al in 22 public hospitals of Kenya also found error in dosages, 11.6% prescriptions had overdose of Benzylpenicillin and 18.5% had overdose of Gentamicin(72).

High number of antibiotics

Suryawanshi et al in India concluded that 70.7% of neonates had received the antibiotic therapy. The preterm and out born neonates received high numbers of antibiotic prescriptions(73). A hospital based retrospective cohort study was done in South Africa in 2005, 195 neonates were enrolled into the study. The study showed that antibiotics were prescribed to 144(74%) neonates, 104(72%) had single antibiotic prescribed and 40(28%) had two or more antibiotics prescribed.(74). According to Schellack et al in South Africa, 19 different antibiotics were prescribed for 77 patients (81%). The antibiotics were administered for ≥10 days in 58%(75).

Adverse effects of prolonged antibiotic therapy

A prospective study done by Afjeh SA et al in Iran from 2011 to 2012, concluded that risk factors for prolonged antibiotic therapy were VLBW, maternal illness, chorioamnionitis, multiple pregnancy, non-invasive ventilation and mechanical ventilation; prolonged antibiotic therapy was associated with late onset sepsis, necrotising enterocolitis, prolonged hospital course and mortality(76).

A retrospective cohort analysis of extremely low birth weight infants done by Cotton et al. concluded that empiric antibiotics were administered for > 5 days to neonates with negative cultures in 27% - 85% of neonatal centres with the median duration of treatment varying from 3 to 9.5 days ($P < .001$). Prolonged duration of empiric antibiotic therapy was more likely to be associated with necrotising enterocolitis or death(77). The main challenge is not starting antibiotics, but its continuation without any evidence.

2.6 OUTCOME

Neonatal sepsis is associated with high morbidity and mortality. Neonates deteriorate very fast if timely interventions are not done. Musoke et al in NBU at KNH showed overall neonatal mortality of 24.6%, of these 95.6% of the deaths were in preterm while low birth weight in general contributed to 93.5% of the deaths. Immaturity, respiratory distress, infections and perinatal asphyxia were major causes of morbidity and mortality(32). A study done by Simiyu et al at KNH showed overall mortality of 57.4%. The major causes of death were suspected sepsis, pneumonia, dehydration and hypothermia (71). Kumar et al showed high mortality in neonates with sepsis as compared to neonates without sepsis(28). Early diagnosis and treatment has been shown to improve outcome.

2.7 STRATEGIC IMPORTANCE & EXPERIENCE AT KNH

- KNH is a big training institution, adherence to the guidelines and proper documentation impacts on students.
- KNH is a busy hospital with heavy workload. It has complicated cases because of referrals.
- There are constraints on continuous supply of antibiotics.

CHAPTER 3: STUDY JUSTIFICATION AND UTILITY

Neonatal sepsis is a major contributor of morbidity and mortality globally. Due its subtle and non-specific presentation clinicians usually commence antibiotics empirically based on risk factors and physical examination. Antibiotics should be discontinued within 48 – 72 hours, if the neonate remains clinically stable during this period, blood culture is negative or the haematological investigations done are not suggestive of sepsis(2). Adverse outcomes such as invasive candidiasis, increased antimicrobial resistance, necrotising enterocolitis, late onset sepsis and death can occur by both prolonged treatment with empirical antibiotics and use of broad-spectrum antibiotics(20,75). If initial suspicion of neonatal sepsis was not strong, blood culture is negative and clinical condition of the neonate is improving, clinicians should aim to treat neonatal sepsis with short periods of narrow-spectrum antibiotics. Etiologic agents associated with neonatal sepsis are often susceptible to narrow-spectrum antibiotics. The treatment of choice and duration is usually depends on the centre rather than predisposing factors for sepsis or severity of illness(1).

Following the last review of the Kenyan guidelines in February – 2016, there has not been an audit on antibiotic use for neonatal sepsis in the NBU of KNH. Aim of this study is to audit antibiotic prescribing practices. Adherence to guidelines has been shown to improve outcome and to reduce unnecessary antibiotic exposure. The eventual goal is rational use of antibiotics and cost effective treatment(78,79). Appropriate antibiotic use will improve outcome and prevent antibiotic misuse and hence antibiotic resistance(3,4). Recognition of antibiotic prescribing practices will improve our knowledge, inform our ways of practices and help correct errors.

CHAPTER 4: STUDY QUESTIONS AND OBJECTIVES

4.1 STUDY QUESTIONS

1. What are the antibiotic prescribing practices for neonatal sepsis at the New Born Unit in Kenyatta National Hospital?
2. What is the outcome of Neonatal sepsis among neonates admitted to the New Born Unit in Kenyatta National Hospital?

4.2 OBJECTIVES

1. To audit the antibiotic prescribing practices in Neonatal Sepsis against recommended Kenyan guidelines among neonates admitted to the NBU at KNH.
2. To determine the primary outcome vital status (alive/dead) of Neonatal Sepsis within 7 days among neonates admitted to the NBU at KNH.

CHAPTER 5: RESEARCH METHODOLOGY

5.1 STUDY DESIGN:

This was a prospective audit.

5.2 STUDY PERIOD:

The study was carried out over period of 2 months.

5.3 STUDY SITE:

The study site was the NBU of Kenyatta National Hospital. KNH is the national tertiary referral and teaching hospital located in Upper hill, 4 kilometres from the central business district in the capital city of Kenya. Approximately 20-30% of patients are referred from other facilities. All the sick neonates born in KNH are admitted to NBU. NBU also admits those born elsewhere in the first 24 hours of life and handles transfers from other hospitals even if more than 24 hours. The average admission rate is estimated to be 250 neonates per month. There are 45 cots, 7 incubators and 6 mechanical ventilators in NBU.

5.4 STUDY POPULATION:

5.4.1 INCLUSION CRITERIA:

- Neonates aged 0 day to 28 days who are started on any antibiotics.
- Neonates being admitted to KNH NBU.
- Neonate whose parents/guardian has given informed written consent for inclusion into the study.

5.4.2 EXCLUSION CRITERIA:

- Neonates with birth asphyxia.
- Neonates with major congenital malformations.
- Referred neonates who have received antibiotics for >48 hours.
- Any neonate whose parent/guardian declined to give informed written consent for inclusion into the study.

5.5 CASE DEFINITION:

Perinatal risk factors for early onset sepsis:

Appearance of any of the following perinatal risk factors is associated with development of EONNS.

- Intrapartum maternal fever ≥38ºC (100.4º)
- Prolonged rupture of membranes (> 18 hours)
- Difficult or prolonged labour (>10hours for primiparous, >8 hours for multiparous)
- Foul smelling liquor
- Chorioamnionitis
- Discharge per vagina
- Low birth weight (< 2500g)

Clinical features suggestive of neonatal sepsis:

Presence of any one of the following clinical features is suggestive of neonatal sepsis.

- Refusal to breastfeed or feeding intolerance
- Lethargy or change in level of activity
- Convulsions
- Bulging fontanel
- Hypothermia or hyperthermia
- Apnoea
- Signs of respiratory distress(severe chest wall indrawing, tachypnoea or fast breathing, grunting, cyanosis or decreased oxygen saturation)
- Jaundice within 24hrs of birth
- Pallor
- Septic spots on the skin or septic umbilicus

5.6 SAMPLE SIZE CALCULATION:

The Sample Size was determined using Fischer's Formula:

From the study done by Kithinji et al, the estimated prevalence of antibiotic prescription error was found to be around 37.5%(70).

The calculation was as follow using formula for sample size estimation for infinite population:

$$n = \frac{z^2\, p(1-p)}{e^2} = \frac{1.96^2 \times 0.37(1-0.37)}{0.05^2} = \mathbf{358}$$

Population correction factor applied for finite population:

$$n_{\circ} = \frac{n}{1 + [\frac{(n-1)}{total\ population}]} = \frac{358}{1.12} = \mathbf{320}$$

Where: $n_{\circ}$ = corrected sample size

z = z-value (1.96 for 95% confidence level)

p = prevalence of antibiotic prescription error (Kithinji et al = 0.37)

e = confidence interval, expressed as decimal (0.05= ±5 percentage points)

Total population admitted estimated as 250 monthly = 250×12 = 3000

5.7 STUDY TOOLS:

A standardized questionnaire was used for collecting data from the enrolled participants – (see Appendix 12.1).

The questionnaire included:

- The patient's demographic data (age, sex, gestational age, birth weight, mode of delivery, place of delivery).
- An audit on documentation of maternal and neonatal history (risk factors), clinical signs examined, laboratory investigations requested, diagnosis, and antibiotics prescribed (choice, dosage, frequency, duration).
- Daily audit for 5 days to check whether antibiotics were continued stopped or changed to second line based on clinical condition of the neonate.
- Data on outcome of the neonate (alive/dead) diagnosed with neonatal sepsis within 7 days of admission or on discharge.

5.8 STUDY PERSONNEL:

1. The principal investigator – had overseen collection of data together with research assistants. All data collected were entered into computer every 72 hours and on 7th day.

2. Research assistants – these were two clinical officers who were trained on data collection. They were informed about the purpose of the study.

5.9 STUDY OUTCOME:

- Audit on current antibiotic prescribing practices among neonates aged 0 day to 28 days being admitted to NBU at KNH.
    - Indications for starting antibiotics
    - Type of antibiotics
    - Dosage, frequency and duration of antibiotics
    - Review of antibiotics daily for 5 days(whether antibiotics are continued, stopped or changed)
- Outcome (survived/died) of neonates diagnosed with neonatal sepsis within 7 days of admission or on discharge.

5.10 STUDY PROCEDURES:

Screening: We reviewed the records of all the neonates admitted daily in order to identify those that were eligible for the study.

Neonates who met the inclusion criteria were enrolled into the study.

Sampling: Consecutive sampling was done until the sample size was achieved.

A written informed consent was obtained from the parent/guardian after explaining about the study, its benefits and risks, in English or Kiswahili.

Once the patient was enrolled into the study, demographic data were written down on the questionnaire. This included study identity number, age, sex, gestational age, birth weight, mode of delivery, place of delivery and if they were referred from any health facility. Files (admission records) were audited for documentation of maternal and neonatal history (risk factors), clinical signs examined, laboratory investigations requested, diagnosis, and antibiotics prescribed (choice, dosage, frequency, duration) by using the assessment tool. All the information was written down on the questionnaire.

The 5-day record of the neonate was reviewed to include the duration of treatment and to check whether antibiotics were continued, stopped or changed to second line based on clinical condition of the neonate.

Outcome (survived/died) of the neonate diagnosed with neonatal sepsis also was determined within 7 days of admission or on discharge by daily review of the files.

1. **Confidentiality and privacy:**

All patient information was handled with strict confidentiality. The data were stored in confidentiality preventing inappropriate use of data by use of passwords. Patients were identified by unique study number; their names did not appear on collected data.

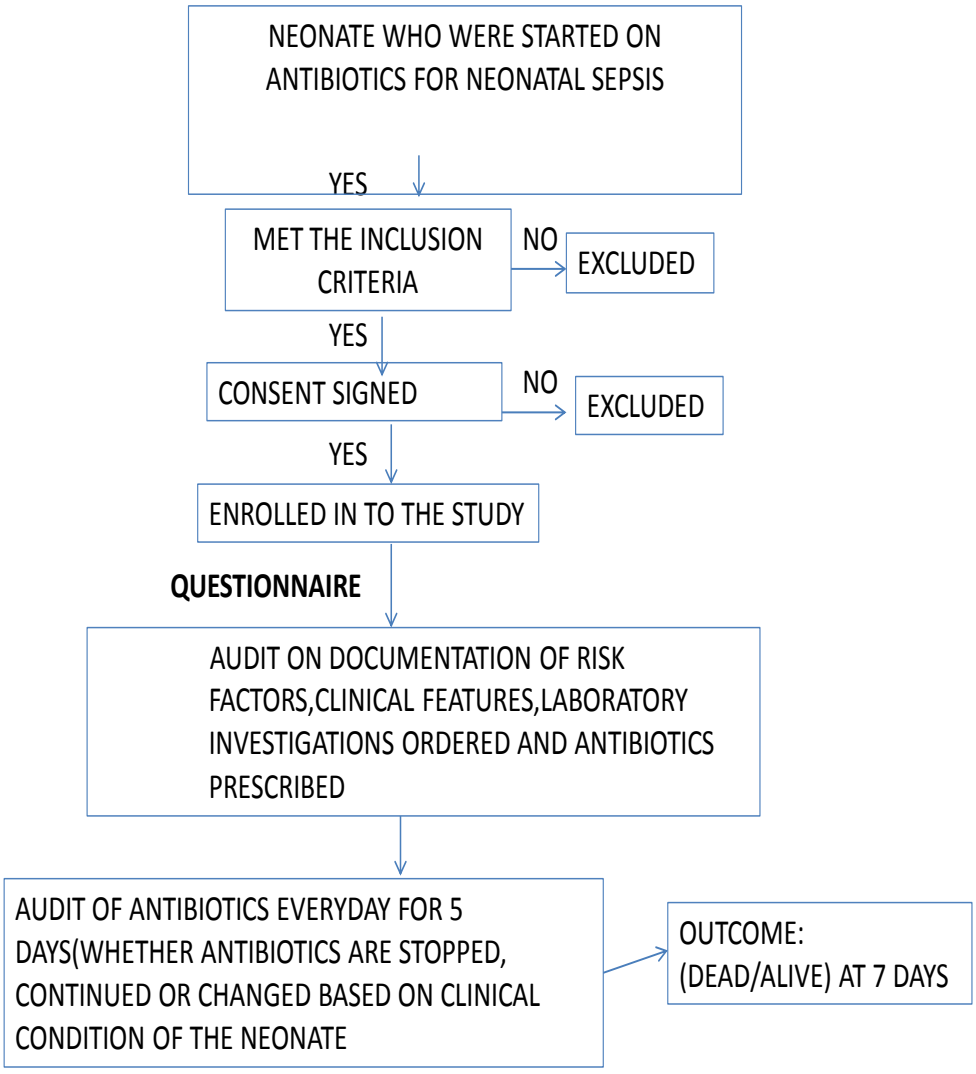
2. **Safety of medical records:**

Patient records were not moved out of NBU; relevant data were abstracted and entered into questionnaires which were stored in lockable cabinets. All electronic versions of the data were protected by pass words with restricted access.

3. **Non interruption of services:**

Data were collected after daily ward round and after giving treatment to prevent interruption of work.

5.11 Figure 8: STUDY FLOWCHART



5.12 DATA COLLECTION, MANAGEMENT AND ANALYSIS

5.12.1 DATA COLLECTION:

Following selection of study subjects, data were collected from identified neonates whose parent/guardian gave consent, using a questionnaire as described in study tool (see section 6.7).

5.12.2 DATA MANAGEMENT:

Data were checked for completeness, accuracy, and consistency. Collected data were recorded in the computer storage program MS-EXCEL at the end of 7^{th} day of follow up of the enrolled participant. Data verification was done manually by proof reading. The data were stored in confidentiality preventing inappropriate use of data by use of passwords. Only the principal investigator and research assistants were able to access data. Data were protected throughout the data lifecycle from creation to destruction and prevent unauthorized sharing. The stored data were readily available whenever it was needed for analysis.

5.12.3 DATA ANALYSIS:

Data analysis was done by STATA software package. Continuous variables were summarised using means (Standard Deviation) and medians (range). Categorical variables were presented as frequency distributions using tables or graphs.

We computed the proportion of neonates whose prescription conforms to the national recommendations. The data collected on the audit of antibiotic prescribing practices were compared with the recommended Kenyan guidelines. The chi square test was used to compare the outcome variable (dead or alive at 7 days) versus categorical variables across two groups by level of guideline adherence. All independent variables were combined to generate regression models to compare effect on the outcome variable. The proportion of correct antibiotic prescribing practices determined 95% confidence interval. The proportion of neonates dead or alive at 7 days or on discharge determined 95 % confidence interval.

5.13 ETHICAL CONSIDERATION

1. Permission was obtained from KNH Ethics and Research Committee to carry out the study. Copies of this Protocol and the consent form was given to the above named committee for written approval prior to commencing the study.

2. A full explanation of the study was given to the parent/guardian and written consent in English or Kiswahili signed by the parent/guardian was obtained to participate in the study.

3. All patient information was handled with strict confidentiality. The data were stored in confidentiality preventing inappropriate use of data by use of passwords. Only the principal investigator and research assistants were able to access data.

4. Patients were identified by unique study number.

5. During auditing of the files, if antibiotic prescription for any neonate was found incorrect then doctor on call was informed.

6. During auditing of the files, if any fault in the management was found the concerned doctor was informed.

7. The overall study findings were availed to the specialists and staff, thereby contributing to the improvement of care delivered to this subset of neonates. The study findings were also presented to the University of Nairobi (UON) Department of Paediatrics and Child Health Academic Staff and Students in fulfilment of the requirements of the MMed Program.

5.14 CONTROL OF BIAS AND ERRORS

1. Measurement bias- the questionnaire was pretested to reduce bias, ensuring the questions were sensitive enough to detect what might be important difference in the variable of interest. Training of the research assistants on the data collection procedure reduced bias.

2. Selection bias- only those who met the eligibility criteria were included in the study. KNH is a tertiary hospital and majority of the patients were referred due to severity of their illness. NBU is a specialised unit so generalisation was a problem.

CHAPTER 6: RESULTS

SOCIODEMOGRAPHIC CHARACTERISTIC OF STUDY POPULATION

A total of 320 infants aged 0 days to 28 days admitted were enrolled in the study. The median age at admission was 1 day (IQR 1-7 days) and 297(92.8%) were aged between 1 – 3 days. Out of the total neonates 170(53.2%) were male and 150(46.8%) were female, almost equal number of male and female. Greatest proportions of neonates were term 157(49.06% with 95% CI 43.5-54.55). Low birth weight neonates were 162(50.7%). Neonates admitted as referral from other health facilities or homes were 134(42%). Neonates delivered by caesarean section and SVD were 160(50%) and 147(46%) respectively, 13(4%) were delivered by breech. Neonates with early-onset sepsis were 297(92.8%), while 23(7.2%) had late-onset sepsis.

Table 5: Socio-demographic characteristics of participants

Variable	Characteristics	Frequency (%) n=320
Gestational age(in weeks)	<28	17 (5.3)
	28 – <32	31 (9.7)
	32 - <37	112 (35)
	37- 40	157 (49.1)
	>42	3 (0.9)
Age at admission(in days)	1 – 3	297(92.8)
	≥4	23(7.2)
Sex	Male	170 (53.2)
	Female	150 (46.8)
Birth weight(in grams)	< 1000	16 (5)
	1000 - <1500	36 (11.3)
	1500 - <2500	110 (34.4)
	2500 - <4000	150 (46.8)
	≥4000	8 (2.5)
Referral from another facility	Yes	134 (42)
	No	186 (58)
Place of delivery	Hospital	307 (96)
	Home	13 (4)
Mode of delivery	SVD	147 (46)
	C/S	160 (50)
	Breech	13 (4)

AUDIT OF DOCUMENTATION OF CLINICAL FEATURES

Complete documentation of clinical features for neonatal sepsis was not done in any of the 320 neonates. The clinical features not documented by clinician on admission were convulsions in 252(41.05%), grunting in 128(20.85%), lower chest wall indrawing in 76(12.4%) and lethargy in 65(10.6%). Signs of respiratory distress were mostly present and documented, because study

population included preterm neonates as well. Refusal to breastfeed was documented in the term neonates admitted from postnatal wards of KNH, only if it was present.

Table 6: Audit of documentation of clinical features

Clinical features(not documented)	**Frequency % (n=320)**
Convulsions	252(41.1)
Lethargy	65(10.6)
Bulging fontanel	35(5.7)
Lower chest wall indrawing	76(12.4)
Grunting	128(20.9)
Cyanosis	24(3.9)
Pallor	18(2.9)
Jaundice	16(2.6)

AUDIT OF DOCUMENTATION OF PERINATAL RISK FACTORS

Overall documentation of perinatal risk factors was very poor. The most commonly documented perinatal risk factors were low birth weight (documented in 100%), prolonged rupture of membranes (documented in 51.6%), foul smelling liquor (documented in 11.2%), chorioamnionitis (documented in 10.2%) and difficult or prolonged labour (documented in 7.8%). Maternal fever (documented in 1.6%) and discharge per vagina (documented in 0.4%) were rarely documented. Only 2(0.6%) had history of maternal intrapartum antibiotics use. Overall 53(16.6%) neonates had maternal risk factors present.

Table 7: Audit of documentation perinatal risk factors

Perinatal risk factors present at birth Frequency (n=320) (%)	**Documented**		**Not documented**
	Present	**Absent**	
Maternal fever >38˚c	3(1)	2(0.6)	315(98.4)
Foul smelling liquor	16(5)	20(6.2)	284(88.8)
Chorioamnionitis	13(4)	20(6.2)	287(89.8)
Discharge per vagina	1(0.4)	0	319(99.6)
Prolonged rupture of membranes	11(3.4)	154(48.2)	155(48.4)
Difficult or prolonged labour	9(2.8)	16(5)	295(92.2)
Received intrapartum antibiotics	2(0.6)	0	318(99.4)
Low birth weight <2500g	155(48.4)	165(51.6)	0

AUDIT OF INVESTIGATIONS DONE ON ADMISSION

Blood cultures were done only in 13(4%) neonates on admission, while haemogram and CRP were done in 224(70%) and 198(62%) respectively. Blood sugar was measured in 26(8%) neonates. Immature to total lymphocyte count and lumbar puncture were not done in any of the neonates.

Table 8: Audit of investigations done on admission

Investigations	**Frequency (%) n =320**
Complete blood count	224(70)
C reactive protein	198(62)
Immature to total lymphocyte count	0
Blood culture	13(4)
Lumbar puncture	0
Blood sugar	26(8)

AUDIT OF ANTIBIOTICS PRESCRIBING PRACTICES

According to Kenyan guidelines (Basic Pediatrics Protocols - Feb2016) recommended first-line treatment for neonatal sepsis is penicillin and gentamycin in combination. Appropriate antibiotics as per the Kenyan guidelines were prescribed in 313(97.8%) of neonates on admission. Ceftazidime and Amikacin were prescribed in 7 neonates, while only Ceftazidime was prescribed in 1 neonate.

Appropriate doses of Penicillin and Gentamicin were given in 310(96.9%) and 282(88%) respectively on admission. The dose of Gentamicin for neonates weighing < 2kgs and aged <7 days is 3mg/kg. Overdose of Gentamicin was observed in such babies.

Table 9: Audit of antibiotics given on admission

Antibiotic use	**Frequency(%) n= 320**
Antibiotics as per Kenyan guidelines on admission	313 (97.8)
Appropriate dose for Penicillin	310(96.9)
Appropriate dose for Gentamycin	282(88)

Appropriate antibiotics doses were not given in 10(3.3%) at 24 hours, in 30(10.9%) at 48 hours, in 24(9.3%) at 72 hours, in 18(8.4%) at 96 hours and in 12(7.7%) due to lack of IV access.

Table 10: Audit on adequate doses of antibiotics for 5 days

Adequate doses of antibiotics received	**Frequency (%)**	**At 24 hrs**	**At 48 hrs**	**At 72 hrs**	**At 96 hrs**	**At 120 hrs**
		(n=300)	**(n=276)**	**(n=258)**	**(n=214)**	**(n=156)**
	Yes	290(96.7)	246(89.1)	234(90.7)	196(91.6)	144(92.3)
	No	10(3.3)	30(10.9)	24(9.3)	18(8.4)	12(7.7)
	Reason	No IV line	No IV line	No IV line	No IV line	No IV line

According to Kenyan guidelines (Basic Paediatrics Protocols - Feb 2016), empiric antibiotics should be given for 48 - 72 hours and maybe discontinued if the neonate remained clinically stable during this period.

At 48 hours - Out of 276, 148(53.62%) neonates improved clinically, yet antibiotics were stopped only in 8(2.9%) and were changed to oral antibiotics in 6(2.17%). Neonates deteriorated clinically were 34(12.32%) and antibiotics were changed for 16(5.8%). Blood culture and CRP was done for 12(3.4%).

At 72 hours - Out of 258, 168(65.12%) neonates improved clinically, yet antibiotics were stopped only in 22(8.53%) and were changed to oral antibiotics in 8(3.11%). Neonates deteriorated clinically were 32(12.4%) and antibiotics were changed for 13(5.03%). Blood culture was done for 10(3.9%), while CRP was done for 16(6.2%).

Table 11: Audit of antibiotic usage over 5 days

	Frequency (%)	**At 24 hrs**	**At 48 hrs**	**At 72 hrs**	**At 96 hrs**	**At 120 hrs**
		(n=300)	**(n=276)**	**(n=258)**	**(n=214)**	**(n=156)**
Condition of the child clinically	Improved	103(34.3)	148(53.6)	168(65.2)	140(65.4)	114(73.1)
	Deteriorated	29(9.7)	34(12.4)	32(12.4)	24(11.2)	12(7.7)
	No change	148(49.3)	83(30)	40(15.5)	35(16.4)	20(12.8)
	Not documented	20(6.7)	11(4)	18(6.9)	15(7)	10(6.4)
Antibiotic usage	Stopped	1(0.35)	8(2.9)	22(8.5)	34(15.9)	40(25.6)
	Continued	298(99.3)	246(89.1)	215(83.3)	156(72.9)	106(68)
	Changed	0	16(5.8)	13(5.1)	16(7.5)	5(3.2)
	Changed to oral	1(0.35)	6(2.2)	8(3.1)	8(3.7)	5(3.2)
CRP done	Yes	0	12(3.4)	16(6.2)	10(4.7)	6(3.8)
	No	300(100)	264(96.6)	242(93.8)	204(95.3)	150(96.2)
Blood culture done	Yes	0	12(3.4)	10(3.9)	8(3.7)	6(3.8)
	No	300(100)	264(96.6)	248(96.1)	206(96.3)	150(96.2)

AUDIT ON ANTIBIOTICS CHANGED FROM PENICILLIN/GENTAMICIN DURING THE 5 DAYS

In 44(13.75%) neonates antibiotics were changed to Ceftazidime and Amikacin and in 3(0.94%) it was changed to Meropenem during 7 days.

Table 12: Audit on antibiotics changed from Penicillin/Gentamicin during 5 days

Antibiotics	Frequency (n = 320)	Percentage (%)
Ceftazidime/ Amikacin	44	13.75
Meropenem	3	0.94

AUDIT OF OUTCOME OVER 7 DAYS

- Overall mortality among 320 neonates admitted was 80(25%) over 7 days as shown in figure 9 below. Mortality among preterm neonates (< 37 weeks gestation) was 70(21.8%).
- Figure 10 shows mortality rate according to time duration. Twenty (25%) neonates died within the first 24 hours, 24 (30%) died within 24 - 48 hours, and 36 (45%) died between 48 hours - 7 days. Out of the neonates who died within 48 hours, 38(11.8%) were preterm.

Figure 9: Overall mortality rate

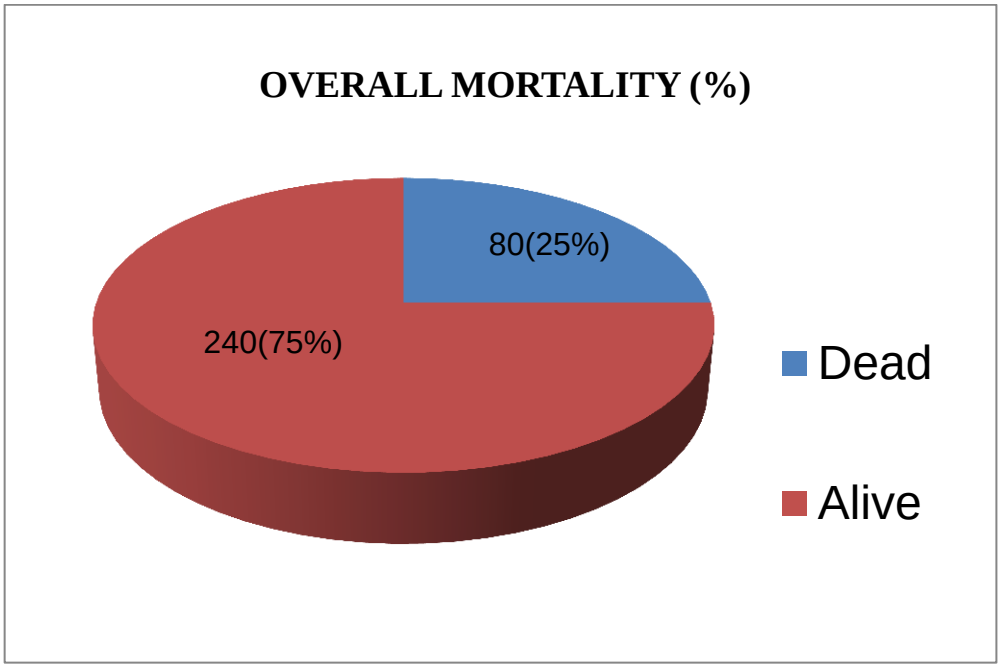
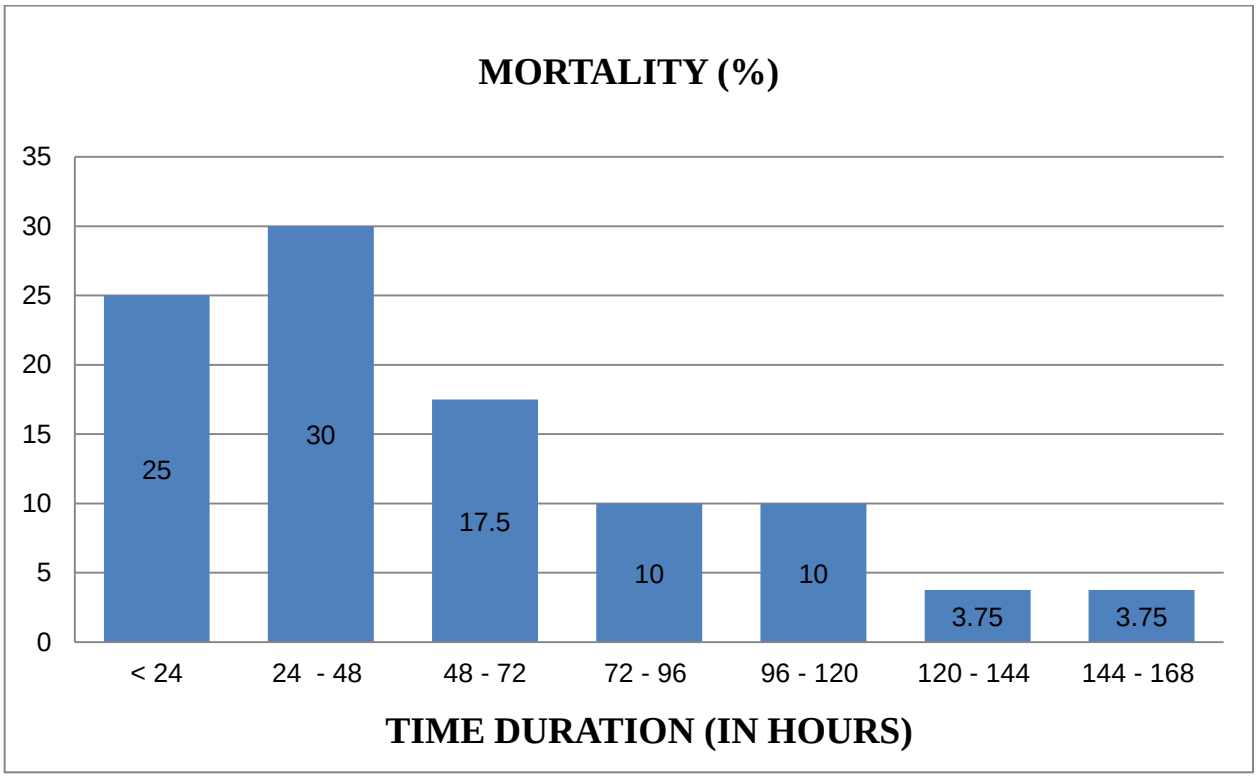


Figure 10: Mortality rate according to time duration



CHAPTER 7: DISCUSSION

This study was carried out to audit antibiotic prescribing practices for neonatal sepsis against recommended Kenyan guidelines in the NBU at KNH. This was the first audit study done in this unit after the Kenyan guidelines were revised in Feb – 2016.

Complete documentation of clinical features and perinatal risk factors for neonatal sepsis was not done in any of the 320 neonates. It was presumed that some clinical features like convulsions, lethargy and refusal to breastfeed were only documented if they were present; it may be because in most cases documentation was not done in a structured neonatal admission record. Refusal to breastfeed was poorly documented because majority of the neonates admitted in NBU were preterm and LBW. Perinatal risk factors were also documented poorly. This may be because most neonates are brought by health care worker directly from labour ward or maternity theatre without adequate history and not accompanied by the mother. The clinicians may also not focus much on the maternal history. A study done by Kithinji et al in general Paediatrics wards also showed poor documentation of clinical features and perinatal risk factors(70). An audit done by Aluvaala et al in 22 public hospitals of Kenya also showed poor documentation of signs and symptoms(72).

According to Simiyu et al in NBU at KNH, blood cultures were done only in 14% of LBW neonates, yet 37% had diagnosis of suspected sepsis. Forty three percent had no laboratory investigations done by the time of death or discharge(71). In our study, we found that rate of blood cultures on admission was very low at 4% as compared to study done by Simiyu et al. The rate of re-evaluation was also very low in our study.

In our study, appropriate antibiotics as per the Kenyan guidelines (Basic Pediatrics Protocols- 2016) were prescribed in 97.8% of neonates on admission, while 2.2% of neonates were prescribed Ceftazidime and Amikacin. Appropriate doses of Penicillin and Gentamicin were given in 96.9% and 88% respectively on admission. Overdose of Gentamicin was observed in neonates weighing <2kgs and aged <7 days. We documented high rate of antibiotic use, may be because half of our study population comprised of preterm and LBW neonates.

According to Kithinji's study in KNH paediatric wards, recommended first line antibiotics were given in 64.4% of neonates, with 37.5% of them having error in the dosages. The rest had either Ceftriaxone, Ceftazidime, Amikacin or Meropenem documented as first line. He also found Gentamicin overdosing in neonates <7days and <2kgs(70). Aluvaala et al also found error in dosages, 11.6% prescriptions had overdose of Benzylpenicillin and 18.5% had overdose of Gentamicin (72). Ototoxicity and nephrotoxicity has been reported by use of Gentamicin(80). Simiyu et al found that in NBU, KNH antibiotic therapy was initiated in 86% of neonates yet 37% of infants suspected sepsis.

Only 13.5% of cases was a change of antibiotics guided by culture and sensitivity reports (71).

From this study we found that there was prolonged unnecessary use of antibiotics in neonates who improved clinically at 48 – 72 hours just like in other studies done in high resource settings. Neonates who improved clinically at 48 hours were 53.62%, yet antibiotics were stopped in 2.9% only. At 72 hours 65.12% neonates improved clinically, but antibiotics were stopped only in 8.53%. The continuation of antibiotics was more inappropriately done than initiation of antibiotics. Earlier discontinuation of antibiotics was an issue, may be because of inability to confirm infection. We should consider other non-infectious causes of diseases in instances when there is no improvement in condition of the neonate while on antibiotics. An Indian study done by Suryawanshi et al, also showed that antibiotic therapy was initiated in 70.7% of neonates. The preterm and out born neonates received high numbers of antibiotic prescriptions. Preterm neonates received high number of antibiotics, probably because of poor immunity, need for intubation and mechanical ventilation and high risk of sepsis(73).

A study done by Slogrove et al in South Africa showed similar results to our study. They found that among the neonates treated empirically, one-third (33.3%) were asymptomatic, antibiotics were continued beyond 24 hours unnecessarily in 38% of EONNS and 28% of LONNS with negative inflammatory markers at 48-72 hours. Neonates treated for > 144 hours during their first antibiotic episode were more likely to require a second antibiotic episode ($p < 0.02$)(74). Schellack et al in South Africa also showed overuse of antibiotics, antibiotics were administered for ≥10 days in 58% (75). The incidence of late-onset sepsis can be decreased by reducing the duration of antibiotics, it does not increase the risk of relapse(81). Our results cannot be compared with local studies, as this was the first audit study on antibiotic prescribing practices in NBU at KNH. According to Schellack et al in South Africa, 19 different antibiotics were prescribed for 77 patients (81%).

An audit done by Abdelrhim et al, in United Kingdom in 2012, demonstrated all 22 could have been managed safely with 36 hours of antibiotics, but they were given antibiotics for > 48 hours(69). A Prospective Surveillance done by Cantey et al in 2011-12 in Texas concluded that 94% of antibiotic use was empiric therapy for suspected infection. When cultures were sterile, antibiotics were stopped only in 63% at 48 hours and 26% received antibiotics for ≥5 days despite sterile cultures. Prolonged antibiotic therapy ≥ 7 days was given for pneumonia and culture-negative sepsis(68). A study done by Afjeh SA et al in Iran also showed prolonged duration of antibiotic for 7-62 days with a mean duration of 24.01 days(76). 94% of antibiotic use was empirical and only 5% of antibiotic use was for culture-positive sepsis.

A retrospective cohort analysis of ELBW done by Cotton et al. concluded that, empiric antibiotics were administered for > 5 days to neonates with negative cultures in 27% - 85% of neonatal centres

with the median duration of treatment varying from 3 to 9.5 days (P < .001) (77). A multicentre study by Cordero and Ayers also reported that antibiotics were started in most neonates with suspected sepsis and negative blood cultures, but no perinatal risk factors or clinical signs explained prolonged administration. Antimicrobial exposure can be reduced by discontinuing empiric antibiotics when blood cultures are negative in asymptomatic ELBW neonates without compromising clinical outcome(82).

We should emphasize on discontinuing empiric antibiotics as soon as is feasible, if the neonate is clinically stable, blood cultures are negative and CRP is normal. Well-designed clinical trials are not done to evaluate the suitable duration of empirical antibiotics in blood-culture-negative sepsis. The only randomised controlled trial done by Saini et al in neonates >30 weeks and >1000 grams with probable sepsis showed that there was insignificant difference in the treatment failure (defined as reappearance of features of sepsis within 15 days of ceasing antibiotics, with laboratory support) rates between short period(48-96 hours) and long period(7 days) of antibiotics(83). Randomised controlled trial by Gathwala et al concluded that antibiotic therapy for 10 days was as effective as 14 days in blood culture-positive sepsis; if by 7^{th} day of treatment the neonate is clinically stable(84).

In this study overall mortality was 80(25%) over 7 days. Mortality among preterm neonates (< 37 weeks gestation) was 70(21.8%). Forty four (55%) neonates died within 48 hours. Out of the neonates who died within 48 hours, 11.8% were preterm. Overall mortality rate was high, which was similar to other local studies done. High mortality rate could be attributed to prematurity related complications and delay in surfactant administration and non-availability of CPAP. Musoke et al in year 1992 in NBU at KNH, showed overall neonatal mortality of 24.6%, of these 95.6% of the deaths were in preterm while low birth weight in general contributed to 93.5% of the deaths. According to this study, the commonest causes of morbidity and mortality were immaturity, respiratory distress, infections and perinatal asphyxia(32). A study done by Simiyu et al in 2004 in NBU at KNH, reported mortality rate of 57.4%, which was higher as compared to our study, was attributed to increased number of risky deliveries at KNH and referral of LBW infants, leading to overcrowding, understaffing, breakdown in infection control standards and insufficient care. The mortality for small for gestational age was 37%(71). Aluvaala et al reported a blanket crude mortality of 17% (180/1065, 95% CI 11% to 24%), with highest case fatality in the ELBW neonates at 88% (14/16, 95% CI 58% to 97%). Sixty one percent deaths occurred within the first 24 hours after admission(72). Kithinji et al in General Paediatrics wards of KNH showed mortality of 5.5%, which was low as compared to our study, because only term and normal weight neonates are being admitted to General Paediatrics wards(70). Were et al in KNH- NBU demonstrated that neonatal survival rate of 62.6% in neonates born < 2000 grams. None of the ELBW neonates survived beyond the neonatal period. He found that over 28% of

the mortality occurred within the first 24 hours, which is comparable to our study, could be due to inadequate intensive care facilities and poor obstetric services(85).

An observational study done in five low-income countries (Kenya, Zambia, Guatemala, India, and Pakistan) and one mid-income country (Argentina) concluded that neonatal death rates ranged from 41 per 1000 births in Pakistan to 8 per 1000 in Argentina. Half the deaths occurred within 24 hours of delivery. In contrast to our study, this study showed 54% of the neonatal deaths were in term babies and 46% in those weighing ≥2500 grams. A prospective study done in Egypt showed mortality rate of 51% for proven early onset sepsis and 42.9% for proven late onset sepsis(27). According to a review article, the mortality rates ranged from 4 to 46% in developed countries and 0.2 to 64.4% in developing countries(86). A prospective study by Baqui et al in India also reported high mortality in prematurity. In their study, 74.8% of deaths occurred due to prematurity in the first week of life, with 30% in the first day of life and >50% of neonatal deaths secondary to sepsis occurred in the first week of life(87).

STUDY LIMITATION

1. Proper documentation was a limitation. This study being an audit (medical records review) only reflected what was documented. Due to poor documentation, may be tasks were done and not documented, thus the results might be affected. To mitigate it a general talk was given on proper documentation.

2. Hawthorne effect: People might have changed their practices when they came to know about the study.

3. Results might be affected, because the study was over short period of time. Longer duration studies should be done in the future.

CHAPTER 8: CONCLUSION, RECOMMENDATION AND CONFLICT OF INTEREST

8.1. CONCLUSION

- There was poor documentation of clinical features, perinatal risk factors and condition of the neonates at the time of change of antibiotics.
- Appropriate antibiotics as per the Kenyan guidelines (Basic Pediatrics Protocols-2016) were given in 97.8% of neonates on admission.
- The rate of investigations to confirm infection was very low. Blood cultures were done only in 4% of neonates on admission and lumbar punctures were not done.
- The continuation of antibiotics was inappropriate.
- Overall mortality was high in neonates at 25% (80). Mortality among preterm neonates (< 37 weeks gestation) was 70(21.8%). Forty four (55%) neonates died within 48 hours.

8.2. RECOMMENDATIONS

1. Proper documentation of perinatal risk factors, clinical features and condition of the neonate on admission and while changing antibiotics is advocated.
2. Full septic screen should be done on admission to confirm infection and while changing antibiotics.
3. We should emphasize on discontinuing empiric antibiotics as soon as the neonate is clinically stable and laboratory tests done are normal.
4. Antibiotic stewardship should be promoted.

8.3. CONFLICT OF INTEREST

There was no conflict of interest.

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APPENDICES

AUDIT OF ANTIBIOTIC PRESCRIBING PRACTICES FOR NEONATAL SEPSIS IN NEW BORN UNIT AT KENYATTA NATIONAL HOSPITAL

Appendix 1: Assessment Tool

Instructions: Tick/circle appropriately as required and fill in the details or measured values where applicable.

Neonate demographic information

1. Study No: _____ 2. Date of data collection: _____

3. Date of admission: _____

4. Time of admission: _____ AM / PM (circle the appropriate)

5. Date of birth: _____

6. Sex: Male Female

7. Gestational age (weeks): _____ 8. Postnatal age (days): _____

9. Birth weight (grams): _____ 10. Admission weight (grams): _____

11. Date of birth: _____

12. Date of discharge/Death: _____

13. Outcome: Discharged Died Continued treatment

14. Place of delivery: Hospital Home

Other facility (specify) _____ No information

15. Mode of delivery: SVD Breech Emergency C/S Elective C/S No information

16. Apgar score: _____ No information

17. Mother's age (years): _____ 18. Parity: _____

19. Diagnosis made: _____

Perinatal risk factors for neonatal sepsis: Maternal and Foetal

Whether following risk factors for neonatal sepsis were noted by clinician or not?

Maternal fever (> 38 degrees C)	Present	Absent	No information
Foul smelling liquor	Present	Absent	No information
Chorioamnionitis	Present	Absent	No information
Discharge per vagina	Present	Absent	No information

Prolonged rupture of membranes (>18 hours)	Present	Absent	No information
Difficult or prolonged labour (>10hours primiparous, >8 hours multiparous)	Present	Absent	No information
Received intrapartum antibiotics	Present	Absent	No information
Low birth weight <2500g	Present	Absent	No information

Clinical features (signs and symptoms) of neonatal sepsis:

Whether following clinical features for neonatal sepsis were noted by clinician or not?

Temperature(℃)	_____		No information
Pulse rate(beats/min)	_____		No information
Respiratory rate(breaths/min)	_____		No information
Refusal to breastfeed or feeding intolerance	Yes	No	No information
Lethargy or change in level of activity	Yes	No	No information
History of convulsions	Yes	No	No information
Bulging fontanel	Yes	No	No information
Apnoea	Yes	No	No information
Tachypnoea or fast breathing	Yes	No	No information
Severe chest wall indrawing	Yes	No	No information
Grunting	Yes	No	No information
Cyanosis	Yes	No	No information
Decreased oxygen saturation	Yes	No	No information
Jaundice within 24hrs of birth	Yes	No	No information
Pallor	Yes	No	No information

Laboratory Investigations

Were the following tests ordered?			
Complete blood count	Yes	No	No information
C reactive protein	Yes	No	No information
Immature to total lymphocyte count	Yes	No	No information
Blood culture	Yes	No	No information
Lumbar puncture	Yes	No	No information
Blood sugar	Yes	No	No information

Other Investigations (specify): 1. 2. 3.

Treatment given at admission

Antibiotic choice	Dose/kg/dose	Frequency/24hours	Route	Number of doses in 1st 24 hours
Penicillin				
Gentamicin				
Ceftriaxone				
Other drugs				
1.				
2.				
3.				

Audit at 24 hours and 48 hours

	At 24 hours	At 48 hours
Documentation of progress	1. Documented? 1)YES_____(go to no.2) 2)NO_____ 2. Clinical condition 1)Improved _____ 2)Deteriorated_____ 3)No change _____	1. Documented? 1)YES_____(go to no.2) 2)NO_____ 2. Clinical condition 1)Improved _____ 2)Deteriorated_____ 3)No change _____
Antibiotics	Did the Patient receive all prescribed doses? 1)YES_____	Did the Patient receive all prescribed doses? 1)YES_____
	2)NO_____ 1. How many doses were missed? _____out of_____doses in 24 hours 2. What was the reason for missing the required doses? i) No IV access_____ ii) Medicine not available_____ iii) Missed by health worker___ iv)Other reasons_____ 3. Were antibiotic continued?	2)NO_____ 1. How many doses were missed? _____out of_____doses in 24 hours 2. What was the reason for missing the required doses? i) No IV access_____ ii) Medicine not available_____ iii) Missed by health worker___ iv)Other reasons_____ 3. Were antibiotic continued?

	i) Yes_____ ii) No_____ 4. Were antibiotics stopped? i) Yes_____ ii) No_____ 5. Were antibiotics changed? i) No_____ ii) Yes_____ (go to 4.) 4. What new antibiotics were given? _____ _____	i) Yes_____ ii) No_____ 4. Were antibiotics stopped? i) Yes_____ ii) No_____ 5. Were antibiotics changed? i) No_____ ii) Yes_____ (go to 4.) 4. What new antibiotics were given? _____ _____
CRP	Was CRP done? 1) YES_____ 1.Measured value_____mg/dl 2) NO_____	Was CRP done? 1) YES_____ 1.Measured value_____mg/dl 2) NO_____
Blood culture	Was Blood culture done? 1)YES_____ RESULTS 1.Positive 2.Negative 2) NO_____	Was Blood culture done? 1)YES_____ RESULTS 1.Positive 2.Negative 2) NO_____

Audit at 72 hours and 96 hours

	At 72 hours	At 96 hours	At 120 hours
Clinical condition	1. Documented? 1)YES_____(go to no.2) 2)NO_____ 2. Clinical condition 1)Improved _____ 2)Deteriorated_____ 3)No change _____	1. Documented? 1)YES_____(go to no.2) 2)NO_____ 2. Clinical condition 1)Improved _____ 2)Deteriorated_____ 3)No change _____	1. Documented? 1)YES_____(go to no.2) 2)NO_____ 2. Clinical condition 1)Improved _____ 2)Deteriorated_____ 3)No change _____

Antibiotics	Did the Patient receive all prescribed doses? 1)YES_____ 2)NO_____ 1. How many doses were missed? _____out of_____doses in 24 hours 2. What was the reason for missing the required doses? i) No IV access_____ ii) Medicine not available_____ iii) Missed by health worker___ iv)Other reasons_____ 3. Were antibiotic continued? i) Yes_____ ii) No_____ 4. Were antibiotics stopped? i) Yes_____ ii) No_____ 5. Were antibiotics changed? i) No_____ ii) Yes_____ (go to 4.) 4. What new antibiotics were given? _____ _____	Did the Patient receive all prescribed doses? 1)YES_____ 2)NO_____ 1. How many doses were missed? _____out of_____doses in 24 hours 2. What was the reason for missing the required doses? i) No IV access_____ ii) Medicine not available_____ iii) Missed by health worker___ iv)Other reasons_____ 3. Were antibiotic continued? i) Yes_____ ii) No_____ 4. Were antibiotics stopped? i) Yes_____ ii) No_____ 5. Were antibiotics changed? i) No_____ ii) Yes_____ (go to 4.) 4. What antibiotics were given? _____ _____	Did the Patient receive all prescribed doses? 1)YES_____ 2)NO_____ 1. How many doses were missed? _____out of_____doses in 24 hours 2. What was the reason for missing the required doses? i) No IV access_____ ii) Medicine not available_____ iii) Missed by health worker___ iv)Other reasons_____ 3. Were antibiotic continued? i) Yes_____ ii) No_____ 4. Were antibiotics stopped? i) Yes_____ ii) No_____ 5. Were antibiotics changed? i) No_____ ii) Yes_____ (go to 4.) 4. What antibiotics were given? _____ _____

CRP	Was CRP done? 1) YES_____ 1.Measured value_____mg/dl 2) NO_____	Was CRP done? 1) YES_____ 1.Measured value_____mg/dl 2) NO_____	Was CRP done? 1) YES_____ 1.Measured value_____mg/dl 2) NO_____
Blood culture	Was Blood culture done? 1)YES_____ RESULTS 1.Positive 2.Negative 2) NO_____	Was Blood culture done? 1)YES_____ RESULTS 1.Positive 2.Negative 2) NO_____	Was Blood culture done? 1)YES_____ RESULTS 1.Positive 2.Negative 2) NO_____

OUTCOME OF NEONATAL SEPSIS IN 7 DAYS (tick appropriate)

1) Alive_____
2) Dead_____
   i.≤24 hours_____
   ii.>24 hours - ≤ 48 hours_____
   iii.>48 hours – 7 days_____
   iv. > cause of death

Appendix 2: Consent document and form

Consent information document in English

Date: _____

Study Title: AUDIT OF ANTIBIOTIC PRESCRIBING PRACTICES FOR NEONATAL SEPSIS IN NEW BORN UNIT AT KENYATTA NATIONAL HOSPITAL

Investigator: Dr.Priti J. Tank

Paediatric resident, University of Nairobi

P. O. Box 46657-00100, Nairobi.

Mobile: 0732972085

Email: priti.tank1984@gmail.com

Supervisors: Professor Rachel Musoke

Associate Professor, Department of Paediatrics and Child Health,

University of Nairobi, P.O. Box 49872.

Mobile number: 0721307160

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Dr. Anjumanara Omar

Lecturer, Department of Paediatrics and Child Health,

University of Nairobi, P.O. Box 49872.

Mobile number: 0734656363/ 0721656350

Email: anjumomar@yahoo.com

Kenyatta National hospital/ University of Nairobi - Ethics and Research Committee

College of Health Sciences

Telephone: (+254-020) 2726300-9, extension 44355

P.O. Box 19676-00202, Nairobi.

Email: uonknh_erc@uonbi.ac.ke

Introduction:

I am a postgraduate student at the University of Nairobi, pursuing studies leading to specialisation in Paediatrics and Child Health. I wish to request for your permission, for your baby to participate in a study that will form part of my degree work. The study will involve evaluation of files for documentation and antibiotic prescription. This will be recorded and analysed for research purposes only.

Purpose of the study:

The purpose of this study is to evaluate the antibiotic prescribing practices for Neonatal Sepsis. It will provide information on the current management of sepsis and the steps that can be taken to improve management of sepsis. The information gathered will help in improving knowledge and correct errors on use and misuse of antibiotics.

Background:

Neonatal sepsis is a major cause of morbidity and mortality all over the world. Early diagnosis and treatment has been shown to improve consequence. However prolonged unnecessary use of antibiotics is associated with adverse consequences. Appropriate antibiotic use will improve consequences and prevent antibiotic misuse and hence resistance.

Study Procedures:

Neonates aged 0 day to 28 days being admitted to NBU, KNH will be included in the study. Files of the enrolled participant will be evaluated for neonatal assessment, investigations requested and antibiotic prescription after obtaining an informed consent or assent. Review of the files will be done at every day for 5 days. The data will be filled in the questionnaire. The outcome of the patient will be recorded within 7 days.

Benefits:

The results of this study will inform clinicians on use and misuse of antibiotics. It will also provide information on the current management of neonatal sepsis. The results of the research will also help clinicians to stop unnecessary use of antibiotics.

Risks:

There will be no harm or risks anticipated to your baby during the study. There will be no invasive procedures carried out in the study that may harm your baby.

Voluntariness:

The study will be fully voluntary. There will be no financial rewards to your baby for participating in this study. One is free to participate or withdraw from the study at any point. Refusal to participate will not affect the management of your baby in any way.

Confidentiality:

The information obtained about your baby will be kept in strict confidence. No specific information regarding your baby will be released to any person without your written permission. We will, however, discuss general overall findings regarding all neonates assessed but nothing specific will be discussed regarding your baby's condition. Your baby's study identity number will be used for follow up in the NBU for 7 days and will not be revealed to anyone.

Problems or Questions:

If you ever have any questions about the study or about the use of the results you can contact the principal investigator, Dr.Priti J. Tank, by calling on 0732972085.

If you have any questions on your rights as a research participant you can contact the Kenyatta National Hospital Ethics and Research Committee by calling 2726300, extension 44355.

Consent form

Investigator: Dr.Priti J. Tank

Paediatric resident, University of Nairobi

P. O. Box 46657-00100, Nairobi.

Mobile: 0732972085

Email: priti.tank1984@gmail.com

Supervisors: Professor Rachel Musoke

Associate Professor, Department of Paediatrics and Child Health,

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Email: uonknh_erc@uonbi.ac.ke

I _____having received adequate information regarding the study research, benefits and risks hereby AGREE / DISAGREE (Cross out the appropriate) to participate in the study with my child. I understand that our participation is fully voluntary and that I am free to withdraw at any time. I have been given adequate opportunity to ask questions and seek clarification on the study and these have been addressed satisfactorily.

Parents/Guardian's Signature: _____Date_____

I _____ declare that I have adequately explained to the above participant; the study procedure, benefits and risks and given him /her time to ask questions and seek clarification regarding the study. I have answered all the questions raised to the best of my ability.

Investigator's Signature_____Date_____

Consent information document in Kiswahili

Tarehe: _____

<u>MADA YA UTAFITI</u>: MKAGUO WA MAAGIZO YA DAWA YA UGONJWA WA WATOTO WACHANGA KATIKA HOSPITALI YA TAIFA YA KENYATTA KATIKA WADI YA WATOTO WACHANGA.

<u>Mtafiti Mkuu:DrPriti J. Tank</u>

Mwanafunziwa shahada kuu ya matibabu maalum ya watoto,

Chuo Kikuu cha Nairobi, Sanduku - 46657-00100, Nairobi.

Simu ya mkononi: 0732972085

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Sanduku - 19676 - 00202, Nairobi.

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<u>Utangulizi:</u>

Mimi ni mwanafunzi mmoja wa udhamili katika Chuo Kikuu cha Nairobi, kutafuta masomo na kusababisha utaalamu katika watoto. Ningependa kuomba ruhusa yako, kushiriki kwa mtoto wako katika utafiti ambawo ni sehemu ya kazi yangu shahada. Utafiti itahusisha ukaguzi wa faili kwa kumbukumbu na maagizo antibiotiki. Hii itakuwa kumbukumbu na kuchambuliwa kwa madhumuni ya utafiti tu.

<u>Madhumuni ya utafiti:</u>

Madhumuni ya utafiti huu ni kukagua shughuli na maagizo ya antibiotiki kwa maambukizi ya watoto wachanga dhidi ya miongozo iliyopendekezwa Kenya kati ya watoto waliozaliwa na waliokuwa kwa wadi ya watoto wachanga katika KNH na kuamua matokeo ya maambukizi ya watoto wachanga katika siku saba. Taarifa zilizokusanywa zitasaidia katika kuboresha elimu na kusahihisha makosa juu ya matumizi na matumizi mabaya ya antibiotiki.Itatoa taarifa juu ya usimamizi wa sasa wa maradhi na

hatua ambazo zinaweza kuchukuliwa ili kuboresha usimamizi.

Maswala ya msingi:
Maambukizi ya Watoto wachanga ni sababu kubwa ya maradhi na vifo duniani kote. Utambuzi wa mapema na tiba umeonyesha kuboresha matokeo. Hata hivyo muda mrefu wa matumizi yasiyo ya lazima ya antibiotiki ina husishwa na matokeo mabaya.

Utaratibu wa Utafiti:
Watoto wachanga kutoka siku ya kuzaliwa hadi siku ishirini na nane waliyo kwenye wadi maalum katika KNH, watakuwa kwenye utafiti. Faili za washiriki waliojiunga zitakuwa zikikaguliwa kwa ajili ya upimaji wa utotoni, uchunguzi na antibiotiki baada ya kupata kibali sahihi au kutiwa saini. Ukaguzi utafanyika kwa siku tano kila siku. Matokeo yatajazwa katika karatasi. Matokeo ya mgonjwa yatarekodiwa katika siku ya saba.

Faida:
Matokeo ya utafiti huu yatawezesha kuendeleza maarifa juu ya matumizi mabaya ya antibiotiki. Pia kutoa taarifa juu ya usimamizi wa sasa wa maambukizi ya utotoni.

Hatari:
Hakutakuwa madhara au hatari kwa mtoto wako wakati wa utafiti. Hakutakuwa taratibu vamizi kufanyika katika utafiti ambayo inaweza kumuumiza mtoto wako.

Kujitolea:
Utafiti huo utakuwa kikamilifu hiari. Hakutakuwa tuzo ya fedha kwa mtoto wako kwa ajili ya kushiriki katika utafiti huu. Kukataa kushiriki hakutaathiri usimamizi wa mtoto wako kwa njia yoyote.

Siri:

Taarifa zilizopatikana kuhusu mtoto wako zitawekwa katika ulinzi mkali. Hakuna taarifa maalum kuhusu mtoto wako itatolewa kwa mtu yeyote bila idhini yako kwa maandishi. Sisi, hata hivyo, tutajadiliana kwa ujumla matokeo ya kuhusu watoto wachanga wote lakini hakuna kitu maalum yatajadiliwa kuhusu hali ya mtoto wako. Kitambulisho maalum ya mtoto wako itatumika kwa ajili ya kufuatilia katika wadi ya watoto wachanga kwa siku saba na sikuwa wazi kwa mtu yeyote.

Matatizo ama maswali:
Kama utakuwa na maswali yoyote kuhusu utafiti au juu ya matumizi ya matokeo unaweza kuwasiliana na mpelelezi mkuu, Dr. Priti J. Tank, kwa kupiga simu nambari 0732972085.
Kama una maswali yoyote kuhusu haki yako kama mshiriki wa utafiti unaweza kuwasiliana nasi Prof M.L. Chindia, secretary, Kenyatta National Hospital, Maadili na Utafiti wa Taifa kwa kupiga 2726300, uganisha 44102.

FOMU LA KUTOA IDHINI YA KUSHIRIKI KATIKA UTAFITI

Mtafiti :Dr Priti J. Tank

Mwanafunziwa shahada kuu ya matibabu maalum ya watoto,

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Barua pepe: uonknh erc@uonbi.ac.ke

Mimi_____baada ya kupokea taarifa za kutosha kuhusu utafiti, faida na hatari hili NIMEKUBALI / NIMEKATAA (ondoa isoyofaa) kushiriki katika utafiti wa mtoto wangu. Naelewa kwamba ushiriki wetu ni kwa hiari yetu na ya kwamba mimi niko huru kutoka wakati wowote. Nimepewa fursa ya kutosha kuuliza maswali na kutafuta ufafanuzi kuhusu somo hili na kushughulikiwa kwa kuridhisha.

Sahihi ya Mazazi / Mlezi: _____Tarehe_____

Mimi _____ natangaza kwamba nilielezea kwa kutosha kwa mshiriki juu ya utaratibu wa utafiti, faida na hatari, na amepewa muda wake kuuliza maswali na kutafuta ufafanuzi kuhusu somo. Mimi nikamjibu maswali yote aliyotoa kwa kadri ya uwezo wangu.

Sahihi ya Mpelelezi _____Tarehe_____

Appendix 3: BUDGET

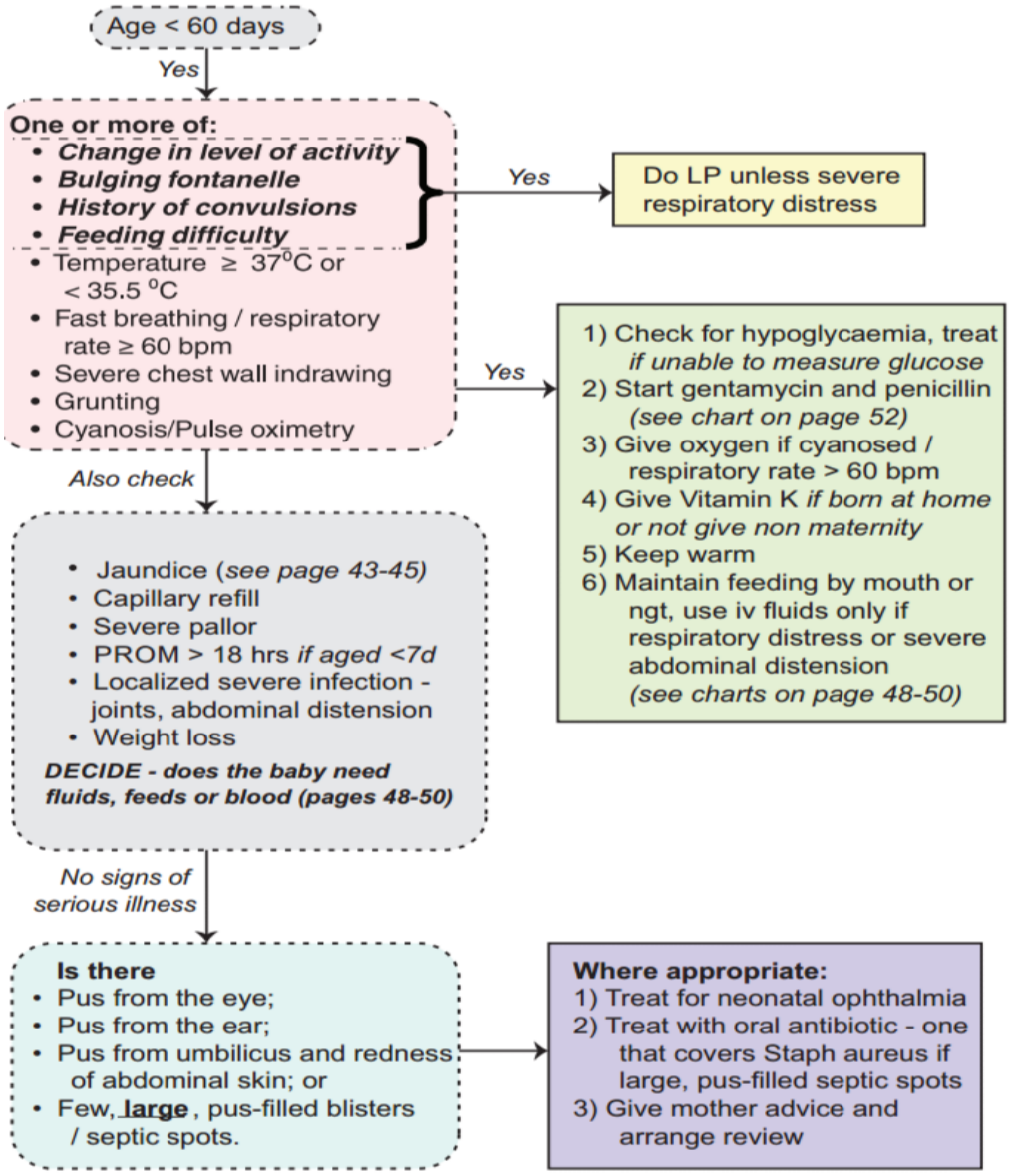
CATEGORY	REMARKS	UNITS	UNIT COST (KSH)	TOTAL COST (KSH)
Proposal development	Proposal copies	10	700	7000
Data collection	Questionnaire	200	100	20000
	Stationery packages (pens, file, staple, paper punch, folder)	2	1000	2000
	Research assistants(2)	100/questionnaire	100 x 200(questionnaire)	20000
Data analysis	Statistician	1	35000	35000
Poster	Printing	1	2000	2000
Thesis write up	Printing thesis	10	1000	10000
Contingency funds				20000
Total				116000

Appendix 4: TIME FRAME

NUMBER	ACTIVITY	ESTIMATED TIME
1	Proposal development and presentation.	November 2016-June 2017
2	Submission of proposal for ethical approval.	July - August 2017
3	Pretesting and seeking permission.	June -July 2017
4	Data collection.	September - December 2017
5	Data analysis.	January - February 2018
6	Thesis writing	February - March 2018
7	Thesis submission	March- April 2018

Neonatal Sepsis / Jaundice

see page 52 for Neonatal Antibiotic doses



Antibiotic prophylaxis

Antibiotic prophylaxis (Benzyl Penicillin and Gentamicin standard dose) should be given as soon as possible after birth to all newborns (term and preterms) with any one of the following risk factors:

- Prolonged Rupture of Membranes (PROM)* >18 hours
- A mother with fever (Temperature > 38º C)
- Suspected or Confirmed chorioamnionitis
- Mother being treated for sepsis at any time during labour or in the last 24 hours before and after birth.

- Treatment should be given for 48-72 hours (at least 4 doses of Penicillin + 2 doses of gentamicin) and may be stopped if the baby has remained entirely well during this period.
- Where possible initiate laboratory investigations immediately but DO NOT withhold antibiotics
- If there are no risk factors then DO NOT initiate antibiotics treatment. A well-baby born preterm < 37 wks or Low birth weight does not require antibiotic treatment

Notes

Duration of treatment for neonatal / young infant sepsis

Problem	Days of treatment
Signs of young Infant Infection in a baby breast feeding well.	▪ Antibiotics could be stopped after 48 hours if all the signs of possible sepsis have resolved and the child is feeding well **and** LP, if done, is normal. ▪ Give oral treatment to complete 5 days in total. Advise the mother to return with the child if problems recur.
Skin infection with signs of generalised illness such as poor feeding	▪ IV / IM antibiotics could be stopped after 72 hours if the child is feeding well without fever and has no other problem **and** LP, if done, is normal. ▪ Oral antibiotics should be continued for a further 5 days.
Clinical or radiological pneumonia.	▪ IV / IM antibiotics should be continued for a minimum of 5 days or until completely well for 24 hrs. ▪ For positive LP see below.
Severe Neonatal Sepsis	▪ The child should have had an LP. ▪ IV / IM antibiotics should be continued for a minimum of 7 days or until completely well if the LP is clear
Neonatal meningitis or severe sepsis and no LP performed	▪ IV / IM antibiotics should be continued for a minimum of 14 days. ▪ If Gram negative meningitis is suspected treatment should be iv for 3 weeks.