

**ROLE OF SERIAL C- REACTIVE PROTEIN IN DETERMINING DURATION  
OF ANTIBIOTIC USE FOR NEONATES WITH SUSPECTED NEONATAL  
SEPSIS: A RANDOMISED CONTROL TRIAL**

**A DISSERTATION PRESENTED IN PARTIAL FULFILLMENT FOR THE  
DEGREE OF MASTERS OF MEDICINE (PEDIATRICS AND CHILD HEALTH),  
UNIVERSITY OF NAIROBI**

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## **DECLARATION**

### **Student Declaration**

I declare that this dissertation is my original work and has not been presented in any other university or institution for the award of the degree or any academic credit.

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## **DEDICATION**

I dedicate this work to my parents, to whom I am eternally grateful to; as well as my siblings and my husband.

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## ABBREVIATIONS

CRP	C - reactive protein
CSF	Cerebrospinal fluid
EONNS	Early Onset Neonatal Sepsis
IL-1	Interleukin-1
IL-6	Interleukin-6
KNH	Kenyatta National Hospital
LONNS	Late onset neonatal sepsis
MDG	Millennium development goals
NBU	New born unit
NICE:	National Institute for Health and Care Excellence
NICU	Neonatal intensive care unit
NNS	Neonatal sepsis
NPV	Negative Predictive Value
PCT	Procalcitonin
PMN	Polymorphonuclear leucocytes
PPV	Positive predictive value
PROM	Premature rupture of membranes
RBC	Red blood cell
TNF	Tumour necrosis factor
WBC	White blood cell
WHO	World health organization

## DEFINITION OF TERMS

- 1. Apnoea:** Cessation of breathing for more than 20 seconds accompanied with bradycardia.
- 2. Feed intolerance:** Presence of at least three of following: gastric residual volume of more than 50% of previous feeding volume, emesis of 50% or more of previous feeding volume, abdominal distension and absence of occult blood in stool.
- 3. Hypothermia:** Low body temperature - below 36°C rectal.
- 4. Hyperthermia:** Raised body temperature - above 37.5°C rectal.
- 5. Meconium aspiration syndrome:** Respiratory distress in an infant born through meconium-stained amniotic fluid whose symptoms cannot be otherwise explained.
- 6. Prematurity:** Neonate delivered before 37 completed week's gestational age.
- 7. Tachypnoea:** A respiratory rate of more than 60 per minute.
- 8. Severe birth asphyxia:** Umbilical artery metabolic or mixed respiratory-metabolic acidemia with pH less than 7.00, persistent Apgar score of 0 to 3 for more than 5 minutes, neonatal neurological sequelae, such as seizures, coma or hypotonia (neonatal encephalopathy) and multi organ system dysfunction.

## **ABSTRACT/ EXECUTIVE SUMMARY**

### **BACKGROUND:**

Neonatal sepsis continues to be an important contributor to infant mortality and subsequently under five child mortality in Kenya. Diagnosis of neonatal sepsis can be challenging due to nonspecific signs and symptoms thus inflammatory markers such as C- reactive protein has been shown to be a useful indicator for diagnosis of neonatal sepsis.

Previous studies show that serial C reactive protein can be used to reduce the duration of antibiotic treatment for neonates with suspected neonatal sepsis. This would lead to decreased duration of hospital stay, cost benefit to the patient and prevent emergence of antibiotic resistance strains of bacteria.

### **OBJECTIVES:**

To determine the utility of serial CRP in determining duration of antibiotic treatment for neonates with suspected neonatal sepsis in New Born Unit at Pumwani Maternity Hospital.

### **METHODS:**

A randomized control trial was conducted and neonates were randomly assigned by block randomization. Patients in the control group were treated with antibiotics according to national health guidelines. Serial CRP was done for patients in the intervention group; antibiotics were stopped once two normal CRP levels 24 hours apart were attained. Mean duration of antibiotic treatment duration were analyzed using student t test, hospital readmission rates one week post discharge was analyzed using Fishers' exact test.

**RESULTS:**

A total of 120 patients were recruited, A total of 120 patients were recruited, 66 males and 54 female patients. Sixty patients were assigned to each arm. Majority of the patients had early onset neonatal sepsis, with only 2 patients having late onset neonatal sepsis.

The mean duration of treatment in the intervention group was 6 days and 5.1 days in the control group ( $p=0.041$ ). On per protocol analysis the mean duration of antibiotic treatment in intervention group was 5.9 days and 5.1 days in the control group ( $p = 0.08$ ).

There were 4 readmissions within one week of discharge in the control group with none in the intervention group ( $p=0.119$ ).

**CONCLUSION:**

There was a statistically significant difference in the duration of antibiotic therapy in both groups; however there were no readmissions in the intervention group. CRP guided treatment did not result in reduction of hospital duration for neonates with suspected neonatal sepsis.

**RECOMMENDATIONS:**

We recommend that a larger multi-center study is carried out to objectively study the use of CRP as an adjunct to clinical acumen in duration of antibiotic use.

## **CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW**

### **1.1 Introduction and Epidemiology**

WHO estimates that there are about 5 million neonatal deaths a year, 98% of which are in developing countries (1). Neonatal sepsis is estimated to cause 26% of all neonatal deaths worldwide (2). Neonatal sepsis occurs in 6.5 to 23 per 1000 live births in Africa (1). By comparison, rates reported in the United States and Australasia range from 6–9 per 1000 (1). Neonatal deaths among under-five mortality worldwide has grown from 36 per cent in 1990 to 43 per cent in 2011 (1). Neonatal sepsis continues to be a leading cause of mortality in the developing world including Kenya, in which it is ranked third amongst the causes of neonatal mortality which currently stands at 31/1000 live births (3). A study done in Kilifi Kenya estimated 5.46 cases of neonatal bacteremia per 1000 live births (4).

Sub-Saharan Africa, which accounts for 38 per cent of neonatal deaths globally, has the highest neonatal mortality rate (34 deaths per 1,000 live births in 2010) and has recorded the least improvement over the past two decades (1).

Despite the high burden of disease we have scarce local data on prevalence of neonatal sepsis. Clinicians will diagnose neonates with suspected neonatal sepsis based on history of maternal risk factors and/or clinical criteria. Current clinical practice dictates clinicians to commence on empirical antibiotics as they await blood culture or lumbar puncture results. If no growth of organism is revealed then antibiotics are to be stopped within 48 to 72 hours accordingly to our national health guidelines (5). However in our clinical practice you will still find neonates with

suspected neonatal sepsis completing 7 to 10 days of antibiotics before being discharged home (6).

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Studies done worldwide have shown that using serial CRP levels can shorten antibiotic duration for treatment and subsequently allow for antibiotics to be stopped once they are no longer required (7-11). However, locally only one study has been done on CRP which showed that CRP is an accurate diagnostic indicator of neonatal sepsis with the positive predictive value of 61.5% and negative predictive value of 96.6% (12).

If antibiotics can be stopped once CRP levels normalise, this could lead to decrease misuse of antibiotic administration and ultimately reduction in antibiotic resistance.

WHO defines antimicrobial resistance (AMR) as resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it. Contributing factors such as the use and misuse of antimicrobial drugs when none are required increases development of antibiotic resistant strains of bacteria (13).

Multidrug resistant bacteria causing neonatal sepsis has been increasing in developing countries (1), and local data has shown there has been a rise of antibiotic resistant bacteria during the recent years and this continues to be an important challenge to clinicians (6).

If antibiotics can be stopped once CRP levels normalise, this could lead to a decrease in misuse of antibiotic administration and ultimately reduction in antibiotic resistance.

This could also lead to reduced hospital stay and thereby reducing the chances of

acquiring a hospital acquired infection which is a significant contributor to neonatal sepsis.

Previous studies have demonstrated CRP to be a useful marker to assist in diagnosis of neonatal sepsis however, no study done locally has attempted to demonstrate its use in clinical management of neonatal sepsis primarily in terms of using it to guide the duration of antibiotic treatment. This study attempts to bridge this gap.

## **Literature Review**

### **1.2 Neonatal Sepsis**

Neonatal sepsis by definition is a disease of infants who are younger than one month of age, are clinically ill, and have positive blood cultures. The presence of clinical manifestations differentiates this condition from the transient bacteremia observed in some healthy neonates (14).

Suspected neonatal sepsis can be defined as neonates with clinical features suggestive of sepsis but with no blood culture growth (15). Due to the non-specific nature of these symptoms, neonates may be misdiagnosed as having neonatal sepsis when they have transient tachypnea of newborn or hypothermia for example.

Neonatal sepsis still continues to be a high burden of disease despite advances in research worldwide in terms of investigation and management; in our set up it still ranks third amongst the causes of neonatal mortality and continues to be a major contributor to infant mortality (3).



Neonatal sepsis can be classified into early onset and late onset, in which early onset neonatal sepsis (EONNS) has an onset during the first seven days of life especially the first 72 hours of life and late onset neonatal sepsis (LONNS) occurs after 7 days of life (16).

Predisposing factors of early onset neonatal sepsis includes infection which is acquired from the mother transplacentally, at the time of delivery, or in the early postnatal period and is usually caused by organisms prevalent in the maternal genital tract. In late onset neonatal sepsis infection is usually acquired from the external environment including medical personnel (17).

Center for Disease Control and Prevention (CDC) defines a nosocomial infection as any infection occurring after admission to the NICU that was not transplacentally acquired (16).

In terms of etiology the causative organisms of neonatal sepsis differ in developing countries from those seen in developed countries. Gram negative bacteria predominate; namely *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas* and *Salmonella*. Gram positive organisms include *Staphylococcus aureus*, Coagulase negative *staphylococcus aureus*, *Streptococcus pneumoniae* and *Streptococcus pyogenes* (1).

A retrospective overview of the aetiology of neonates admitted in a tertiary hospital in Nairobi reported that gram-positive organisms were the predominant cause of both early and late onset sepsis; the common isolates were *Staphylococcus epidermidis*

(34%) and *Staphylococcus aureus* (27%). However this being a retrospective study and being conducted in a private hospital, this may not be a true representative of the entire population (18).

### **1.3 Diagnosis of Neonatal Sepsis**

Neonatal sepsis can be defined by both clinical and/or microbiological methods, by positive blood and/or cerebrospinal fluid cultures (1).

#### **Clinical Diagnosis**

Clinical features of neonatal sepsis are non-specific and therefore diagnosing neonatal sepsis continues to be a challenge to clinicians. The diagnosis can be easily missed, study done in KNH by Ng'ang'a et al in 2013 showed that in well appearing new born the prevalence of proven sepsis was 12% and 58% for probable sepsis (19).

Neonatal sepsis is diagnosed based on combination of history of maternal risk factors and clinical signs and symptoms. Study done at KNH in 2011 showed that the most important risk factors for early onset neonatal sepsis were maternal genital-urinary colonisation, bacteriuria and premature rupture of membranes (PROM) (20).

The major risk factors for early-onset neonatal sepsis are preterm birth, maternal colonization with Group beta streptococcus, rupture of membranes of more than 18 hours, and maternal signs or symptoms of intra-amniotic infection (21).

Fetal predisposing factors include low birth weight defined as birth weight of less than 2500 grams, meconium aspiration syndrome and low Apgar score (22). Infant birth weight is inversely related to risk of early-onset sepsis (22).

In addition to predisposing factors, the clinical features which are suggestive of neonatal sepsis according to the young infants clinical signs study group, which assessed clinical signs that predict severe illness in children under age two months in several centres, reported that seven signs were identified as good predictors of severe illness. These included; history of difficulty feeding, history of convulsions, lethargy, tachypnoea of 60 breaths per minute or more, severe chest in drawing, temperature of 37.5°C or more or below 35.5°C (23).

**Table 1: Clinical Criteria for the Diagnosis of Sepsis**

<b>Table 1 Clinical criteria for the diagnosis of sepsis</b>		
	<b>IMCI criteria for severe bacterial infection*</b>	<b>WHO young infant study group†</b>
Convulsions	X	X
Respiratory rate >60 breaths/min	X	X (divided by age group)
Severe chest indrawing	X	X
Nasal flaring	X	
Grunting	X	
Bulging fontanelle	X	
Pus draining from the ear	X	
Redness around umbilicus extending to the skin	X	
Temperature >37.7°C (or feels hot) or <35.5°C (or feels cold)	X	X
Lethargic or unconscious	X	X (not aroused by minimal stimulus)
Reduced movements	X	X (change in activity)
Not able to feed	X	X (not able to sustain suck)
Not attaching to the breast	X	
No suckling at all	X	
Crepitations		X
Cyanosis		X
Reduced digital capillary refill time		

\*Any of the signs listed implies high suspicion of serious bacterial infection.  
†Each symptom or sign is associated with a score. The score indicates the probability of disease.<sup>14 15</sup>  
IMCI, Integrated Management of Childhood Illness.

**Adopted from Neonatal sepsis: an international perspective (1)**

Signs and symptoms of neonatal sepsis are ill-defined, due to the neonate's immature immune system hence laboratory investigations can be done to assist the clinician in diagnosing neonatal sepsis. In cases of respiratory distress syndrome, neonates will also present with respiratory distress and this can be confused with sepsis, and hence laboratory investigations can help to assist the clinician on making an accurate diagnosis of neonatal sepsis.

### **Laboratory Diagnosis**

Gold standard of diagnosis of neonatal sepsis includes growth of microorganisms from blood culture (24). Blood culture needs a minimum of 1ml of blood to be accurate (22).

Yield from blood culture ranges from 19.2% (23) to 32.5% of infants from studies done regionally (25). In some cases blood cultures can be falsely negative due to low blood volumes drawn, single cultures done as well as the prenatal administration of antibiotics.

The decision on whether to do a lumbar puncture is controversial however evidence suggests that lumbar puncture should be performed in any infant with a positive blood culture, infants whose clinical progression or laboratory results strongly suggest bacterial sepsis and infants who initially worsen with antimicrobial therapy (22).

Due to non-specific signs and symptoms of neonatal sepsis inflammatory markers have been introduced to help guide the clinician on accurately diagnosing neonatal sepsis. However till date, no single marker can be used in isolation (26).

Examples of inflammatory markers include; CRP, interleukin 1, interleukin 6 and procalcitonin. CRP is one of the most widely investigated inflammatory markers of infection.

### **Haematological Changes**

Haematological changes used in diagnosis include total white cell count, total neutrophil to immature neutrophil ratio (IT ratio) and platelet count however previous studies have shown that haematological changes are not sensitive or specific for neonatal sepsis. Abnormalities of the white blood cell count, differential and platelet counts are not invariably specific for bacterial infection and normal values do not adequately exclude it (27).

Monroe et al looked at parameters affecting neutrophil counts and reported that perinatal factors other than bacterial disease which significantly alter neutrophil dynamics include maternal hypertension, maternal fever prior to delivery, hemolytic disease and periventricular hemorrhage (28).

Predominantly in early onset neonatal sepsis low white blood cell count, absolute neutrophil count, and high immature-to-total neutrophil ratio correlated with increasing odds of infection, however no complete blood cell count-derived index possesses the sensitivity to rule out consistently early-onset sepsis in neonates (29).

A total leukocyte count of  $<5000$  to  $7500/\text{mm}^3$  can be used to infer the diagnosis of neonatal sepsis. However it is more effective to obtain total leukocyte counts at 6–12 h after birth, as it is more likely to be reliable (30).

Ratio of immature to mature neutrophils known as IT ratio has been used in diagnosis of neonatal sepsis and an I: T ratio of  $>0.2$  is suggestive of sepsis. However, the I: T ratio can be affected by various non-infectious processes like labour, prolonged induction with oxytocin, and prolonged crying.

Components of the white cell count, including absolute neutrophil count (ANC) and IT ratio have been shown to be more valuable for excluding infants without infection rather than identifying new-borns who are infected (30).

### **C- Reactive Protein**

CRP was initially described in 1930 by Tillet and Francis at Rockefeller University (31). They observed a precipitation reaction between serum from patients suffering from acute pneumococcal pneumonia and the extracted polysaccharide fraction C from the pneumococcal cell wall (31). This reaction was not observed when using serum of either healthy controls or the same pneumonia patients once they had improved clinically. In view of the fact that the polysaccharide fraction was a protein, the C-reactive component in the serum was named C-reactive protein (31).

CRP has a key role in the acute-phase response, a physiological and metabolic reaction to an acute tissue injury of different aetiologies (trauma, surgery, infection, acute inflammation) which aims to neutralize the inflammatory agent and to promote the healing of the injured tissue(26).

After trauma or invasion of microorganisms, an acute inflammatory reaction is initiated by activation of local resident cells which stimulates the recruitment and

activation of more inflammatory cells including fibroblasts, leukocytes, and endothelial cells. Once activated, these cells release proinflammatory cytokines including IL-1, TNF alpha, and IL-6. These cytokines generate the production of proteins of the acute-phase response in the liver of which CRP is amongst them (26). The production of CRP in the hepatocytes is primarily induced by IL-6, but can be further increased by synergy with IL-1 (26).

CRP functions as an opsonin, an activator of the classical complement pathway, and has a key role in innate immunity. CRP synthesis rises more in a bacterial infection than a viral infection (12). However it can also rise in other inflammatory conditions for example trauma (32).

CRP levels rises approximately 6 hours after an infectious trigger and peaks at 12-24 hours after onset of infection (22). It has a half-life of 19 hours indicating extremely rapid turnover compared with the majority of plasma proteins (26). CRP double time is 6 hours (33) and CRP levels fall by up to 50% per day when the acute-phase stimulus resolves. The single determining factor for CRP concentration is the synthesis rate, which corresponds to the intensity of the pathological process stimulating CRP production therefore when the stimulus for increased production ceases, the circulating CRP concentration falls rapidly. This makes CRP a useful inflammatory marker to monitor response to treatment.

CRP is decreased at a constant catabolic rate independent of plasma concentration (34). CRP levels have been shown to vary and to be increased in non-infectious conditions such as meconium aspiration syndrome and birth asphyxia hence limiting

their use in such conditions (12). It has also been shown that gestational age (less than 38 weeks) and birth weight (less than 2500 grams) are associated with decreased increase in CRP levels and is postulated to be due to immaturity of the hepatocytes (35). CRP levels however are not affected by the levels of bilirubin (35).

Normal ranges vary of CRP, however a cut off of 5mg/dl was deemed acceptable for local use (12).

A study done by Kumar et al in KNH showed serum CRP is an accurate diagnostic indicator of neonatal sepsis and noted the sensitivity, specificity, predictive values and overall accuracy were better fulfilled in late-onset episodes than for early-onset episodes (12), which could be due to delayed synthesis to inflammatory response (26).

The author also demonstrated that diagnostic utility of CRP in proven sepsis had a sensitivity of 88.9%, specificity of 85%, positive predictive value 61.5%, and negative predictive value 96.6%. Similarly the diagnostic utility of CRP in probable sepsis had sensitivity of 100%, specificity of 82.5%, a positive predictive value of 67.3% and a negative predictive value 100%. Overall accuracy was noted to be 87.1% (12). This demonstrates that CRP is useful to exclude infection with its high negative predictive value.

Serial CRP levels are more useful than a single CRP value in regard to diagnosis of neonates with suspected infection. Study done by Benitz et al demonstrated that two CRP levels <1 mg/dL obtained 24 hours apart, 8 to 48 hours after presentation, indicate that bacterial infection is unlikely (negative predictive accuracy of 99.7% and a negative likelihood ratio of 0.15 for proven neonatal sepsis) (36). If CRP



determinations remain persistently normal, there is strong evidence that bacterial sepsis is unlikely (22).

Study done by Stephan Ehl et al in 1997 sought to determine if CRP was a useful marker for guiding duration of antibiotic therapy. This was a prospective study done on 176 neonates using CRP as a single decision criterion to stop antibiotics use. Their primary outcome measure was number of infection relapses after the primary infection within a four week period. Results showed that using CRP correctly identified 120 of 121 infants as not needing further antibiotics which corresponded to a negative predictive value with respect to further treatment of 99% (95% confidence interval, 95.4% to 99.9) (7).

Other studies done in countries such as India, South Africa and Brazil have shown similar results (8-10).

Study done by Bomela et al in South Africa sought to determine the use of CRP in a developing country. In this study, neonates with suspected neonatal sepsis were recruited; CRP levels were done on day of admission with repeat measurements at 24 and 48 hours after birth. Antibiotic therapy was then stopped in infants who had normal CRP levels. They found that the repeat CRP estimation correctly identified 99 of 100 infants in the study as not requiring further antibiotic therapy (negative predictive value, 99%; 95% confidence intervals, 95.6 to 99.97%). They therefore concluded that the use of serial CRP measurements to guide antibiotic therapy was a safe and practical approach in neonates with suspected sepsis in a developing country.

An intervention study done in Brazil found that the average duration of stay decreased from 16 days to approximately 9 days in neonates with culture proven late onset sepsis with the use of serial CRP (10).

However not all studies have shown such results; a study done in Iraq concluded that CRP could not be used for guiding duration of antibiotic treatment for neonatal sepsis. However this study also noted in their limitations that they had included a small sample size, they measured CRP qualitatively and not quantitatively, the latter being more specific. They also did not have a comparison control group (37).

Similarly a clinical audit done recently in UK after introduction of new NICE guidelines, which included a repeat CRP value at 18-24-hour, showed that serial CRP led to increased number of investigations and also increased duration of hospital stay and cost of treatment (38).

### **Procalcitonin**

Procalcitonin is a precursor protein of calcitonin with no hormonal activity. It is an inflammatory marker produced in the acute phase response, serum concentrations of procalcitonin begin to rise 4 hours after exposure to bacterial endotoxin, peak at 6 to 8 hours, and remain elevated for at least 24 hours (30).

Studies done show that serial procalcitonin determinations allow for shorten the duration of antibiotic therapy in term and near-term infants with suspected early-onset sepsis. However the same author also suggested a larger study was done before reflecting these results in clinical practice (39). A systematic review on procalcitonin

concluded that it has good diagnostic accuracy for neonatal sepsis but due to statistical heterogeneity it has to be interpreted with caution (40).

New areas of research are currently comparing CRP and procalcitonin to determine the more useful marker for guiding duration of antibiotic treatment in management of suspected neonatal sepsis.

### **Interleukin 6**

As mentioned earlier, IL-6 is responsible for the production of CRP, so it was postulated that IL-6 levels would rise before CRP levels. Studies done have shown that IL-6 is a sensitive parameter for diagnosing neonatal bacterial infection and concluded the combination of CRP and IL-6 seems to be the perfect tool for the early diagnosis of neonatal infection (41). However when comparing between use of CRP and IL-6 as a single test one author concluded that CRP continues to be the best single test (42).

The most useful of the three inflammatory markers discussed above in our set up would be CRP, as it is a more readily available investigation and more cost effective.

These inflammatory markers could guide clinicians on when to stop antibiotic therapy where none was required, possible leading to decreased levels of antibiotic resistance.

#### **1.4 Antimicrobial Resistance**

Use of antibiotics when none are necessary can expose neonates to increased adverse drug events for example use of gentamycin which could lead to acute kidney injury and/or ototoxicity. It could also lead to development to antibiotic resistant strains of bacteria, due to the danger of removing useful susceptible organisms and replacing it with resistant organisms(6). Local data suggests antibiotic resistance has been shown to be on the rise (6).

The author demonstrated that resistance to gentamicin was 20 per cent, chloramphenicol 23.6 per cent, and amoxicillin/ampicillin 66.3 per cent. Part of the contributory factors to increased resistance included; non-investigation of infants put on antibiotics (50 per cent of cases); prolonged (73 per cent) and unjustified (41.7 per cent) use of antibiotics (6).

Similarly a retrospective review done in a private tertiary hospital in Kenya demonstrated that for the Gram-positive isolates, resistance to ampicillin was high at 46%. Resistance to the second-generation cephalosporin cefuroxime was also notable among both the Gram positive and Gram-negative isolates at 33.7% and 38.5% respectively.(18)

Study done in Tanzania showed that the overall resistance to the WHO recommended first line antibiotics was 100%, 92% and 42% for cloxacillin, ampicillin and gentamicin respectively(24). Increase in antibiotic resistant organisms leads to increased fatality rates of up to 41 per cent (6).

A policy brief released by Women's and Children's Health Knowledge Hub in January 2013 titled antibiotic resistant sepsis in new-borns and infants: a major threat to achieving Millennium development goal (MDG) 4 stated that the rise in antibiotic resistance could be the reason why we are behind in achieving our target for MDG 4. It also recommended that to minimize unnecessary use and overuse of antibiotics, hospitals could restrict the availability and use of higher generation broad-spectrum antibiotics and introduce procedures to stop antibiotics if bacteria are not found in blood tests which was the aim of this study(43).

## **CHAPTER 2: STUDY JUSTIFICATION AND OBJECTIVES**

### **2.1 Justification**

Neonatal mortality is the leading cause of mortality in children under the age of five years in Kenya out of which neonatal sepsis is ranked third in causes of infant mortality. Due to significant mortality associated with neonatal sepsis, clinicians who suspect neonatal sepsis will diagnose and start empirical antibiotic treatment as they await culture results, which is the ideal current management. However this also condemns many of the neonates who have “probable neonatal sepsis” to exposure to antibiotics when none is required, leading to antibiotic overuse and ultimately poses the risk of development of antibiotic resistant strains of bacteria.

Previous studies done elsewhere have shown that serial CRP can be used to guide response to treatment and help stop antibiotic treatment when none is required. This could lead to decreased duration of antibiotic use; reduced exposure to antibiotics which have toxic side effects and ultimately lead to decreased duration of hospital stay and costs incurred by the patient. Prolonged hospital stay could also lead to acquisition of nosocomial infections, which once acquired will further increase duration of hospital stay, increase costs and has been shown to have higher morbidity.

If this study shows that neonates can be safely discontinued antibiotics using CRP with no immediate adverse outcomes then this can give clinicians confidence to implement and use CRP as part of their management plan for patients with suspected neonatal sepsis. It can also be used to advocate for policies to introduce CRP as a routine investigation to be done on all neonates with suspected neonatal sepsis.

## **Study Objectives**

### **Research Question:**

What is the utility of serial CRP in determining duration of antibiotic treatment for neonates with suspected neonatal sepsis in New Born Unit at Pumwani Maternity Hospital?

### **Study Objectives:**

#### **Broad Objective**

To determine the utility of serial CRP in determining duration of antibiotic treatment for neonates with suspected neonatal sepsis in New Born Unit at Pumwani Maternity hospital.

#### **2.2 Primary Objective**

To compare the duration of antibiotic treatment between neonates with suspected neonatal sepsis randomized to a CRP-guided regimen versus the standard recommended regimen for neonates. In the CRP-guided arm antibiotics will be discontinued for neonates with normalized clinical findings and two consecutive normal CRP levels.

#### **2.3 Secondary Objective**

To compare readmission rates within seven days post discharge between the two arms.

## CHAPTER 3: RESEARCH METHODOLOGY

### 3.1 Study Design

This was a randomized, open label, parallel type controlled trial. Neonates with clinically suspected neonatal sepsis based on maternal and fetal risk factors, and clinical signs and symptoms were recruited and randomized into two groups. Random allocation sequence was done on computer generated slips of paper bearing the allocation, which were kept in serially numbered opaque sealed envelopes. Patients were randomly assigned to either the control arm or to the intervention arm in a 1:1 ratio.

Control group: Neonates in this group were commenced on treatment with antibiotics and completed antibiotics for standard duration of time according to national health guidelines. According to the guidelines, antibiotics may be administered from 3 up to 21 days depending on the severity of the infection and the blood culture results.

Intervention group: Neonates in this group had CRP levels done on admission for baseline values, serial CRP samples were then done on every alternate day. Once CRP values had normalized, a repeat CRP value was done 24 hours later to confirm and antibiotics were then stopped, in concordance with resolution of clinical signs and symptoms.

All patients irrespective of which group they were in were reviewed by consultants and medical officers during the major ward rounds.



Decision to stop antibiotics were be made by them, based on improvement of clinical signs and symptoms which included some of the following:

- ❖ Temperature stability
- ❖ Lack of feeding intolerance
- ❖ Resolution of respiratory distress

CRP value of less than 5 mg/dl was used as a cutoff point which was appropriate for local use (8).

Patients were then followed up after discharge; a one week follow up appointment was given upon discharge. Mothers contact details were taken which enabled us to contact them via telephone, therefore enabling us to monitor our patient's clinical outcome after discharge to determine if any patient was readmitted during that period.

Primary outcome measure was mean duration (number of days) of antibiotic usage.

Secondary outcome measure was number of readmissions after discharge.

### **3.2 Study Population**

Late preterm of more than 35 completed weeks and term neonates aged 0-28 days with clinical features of suspected neonatal sepsis.

**Table 2: Study Population**

Maternal risk factors	Fetal risk factors
Prolonged rupture of membranes more than 18 hours	Low birth weight (< 2500g)
Maternal fever of more than 38 degrees Celsius	Meconium aspiration syndrome
Multiple vaginal examinations (> 4) Foul smelling liquor	Prematurity
Maternal risk factors	Fetal risk factors
Prolonged rupture of membranes more than 18 hours	Low birth weight (< 2500g)
Maternal fever of more than 38 degrees Celsius	Meconium aspiration syndrome
Multiple vaginal examinations (> 4) Foul smelling liquor	Prematurity

### **3.3 Inclusion Criteria**

1. Clinical features in the neonate are non-specific and tend to have multi-organ involvement and can be categorized as follows:

- ❖ A: Apnoea/ tachypnoea/nasal flare/ chest retraction/ cyanosis
- ❖ B: Bradycardia/tachycardia
- ❖ C: Hypotonia/ seizures
- ❖ D: Poor skin colour/ capillary refill > 3 seconds
- ❖ E: Irritability/ lethargy

- ❖ F: Gastric stasis/ diarrhoea/ constipation/ vomiting
- ❖ G: Poor feeding/ hematochezia
- ❖ H: Nonphysiological jaundice/ signs of localized infection

It is preferable to have at least three features from different categories (12). We included patients who had more than or equal to one clinical feature of neonatal sepsis (23).

1. Mothers with access to mobile phones
2. Written Consent from parent/guardian

### **3.4 Exclusion Criteria**

1. Preterm less than 35 completed week's gestational age.
2. Congenital malformations.
3. Meningitis: patients with confirmed cases of meningitis via CSF studies would require longer duration of antibiotic usage and no studies have been done to show if CRP is useful in neonates with meningitis both as a diagnostic marker and as a determinant to antibiotic duration. We excluded any neonate who had neonatal meningitis from the admission diagnosis.
4. Severe birth asphyxia.
5. Low birth weight less than 2000 grams.
6. Meconium aspiration syndrome.
7. Mothers without access to mobile phones.
8. Parents/guardians who refuse consent.

### **Case Definition**

- ❖ Proven sepsis: Defined those whose blood culture yielded pathogenic bacteria.

- ❖ Probable sepsis: Defined those whose clinical and /or CRP findings were consistent with this diagnosis but cultures were negative.
- ❖ No sepsis: Defined those with no clinical or CRP findings attributable to sepsis.

### **3.5 Study Location**

Pumwani Maternity Hospital is a referral maternity hospital located on the east of Nairobi City. The hospital was founded in 1926 by a charitable organization called Lady Griggs Welfare League and was named Lady Grigg Maternity. In 1928 the first permanent building was put up at the hospital and later some extensions were made to give the hospital a bed capacity of 27. Today, it is an obstetric and referral hospital for delivery of expectant mothers in Nairobi and adjoining districts.

It has 354 obstetric beds, 144 baby cots and 2 theatres. Daily normal deliveries are 50 – 100, and caesarean sections are 10 – 15. To date the hospital remains the largest maternity hospital in the country and Sub-Saharan Africa. It is reported to be third busiest maternity hospital in the African continent.

Clinical ward rounds in the new born unit are conducted daily by medical officers and pediatrician consultants twice a week on Tuesdays and Thursdays.

### **3.6 Study Period**

This study was carried out at Pumwani Maternity Hospital between April to September 2015.

### 3.7 Sample Size

Determined by formula used for comparison of two means: (44)

$$n = \frac{2(Z_{\alpha} + Z_{\beta})^2 S^2}{d^2}$$

Where:

$Z_{\alpha}$  = 1.96 (Z statistic representing a Type 1 error rate of 0.05 and 95% confidence level)

$Z_{\beta}$  = 1.28 (Statistic representing Type 2 error in a study with 90% power to detect a difference in mean of 2 days in duration of antibiotic treatment)

S: Standard Deviation estimated at 3, therefore  $S^2 = 3^2$

$\bar{x}_1$ : mean duration of antibiotic treatment in neonates not monitored using serial CRP = 7 (obtained for mean duration of treatment estimated in ward records at KNH)

$\bar{x}_2$ : mean duration of antibiotic treatment in neonates monitored using serial CRP = 5 (representing the desired duration of antibiotic treatment from guideline recommendations) (22)

d: The mean difference between mean 1 ( $\bar{x}_1$ ) and mean 2 ( $\bar{x}_2$ ), therefore  $7 - 5 = 2$

**Solution:**

$$n = \frac{2(1.96 + 1.28)^2 \times 3^2}{2^2} = 48 \text{ per group}$$

$$n = 48 \times 2 = 96$$

48 subjects per group (90% power). An additional 12 participants were added per group to cater for defaulting patients. Consecutive sampling was done.

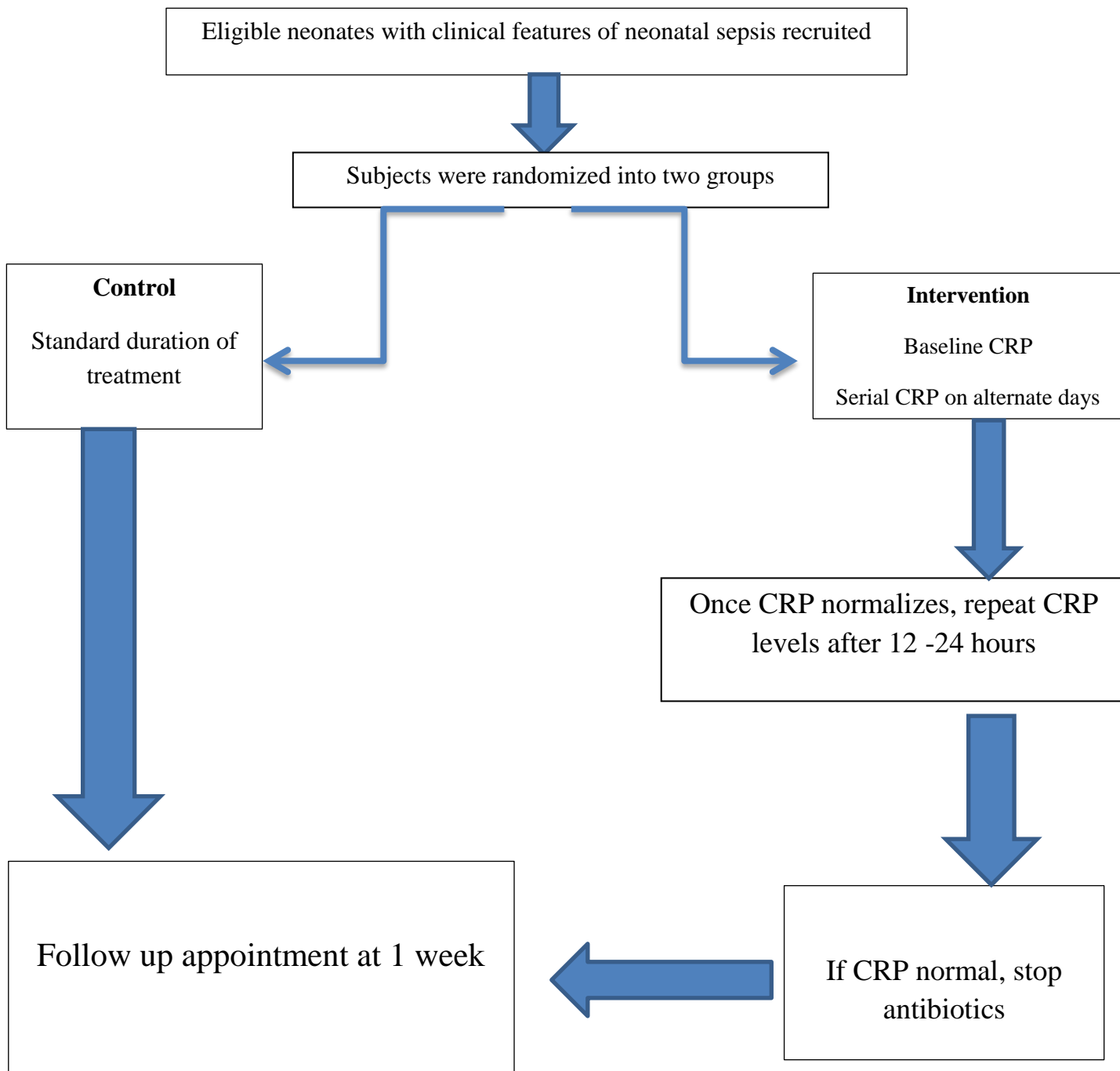
### **3.8 Patient Recruitment Procedure**

Potential study participants were recruited by examining the admission book on a daily basis to identify patients who were admitted with suspected neonatal sepsis. These subjects were then identified and chosen for the study if they met the eligible criteria (inclusion and exclusion). Once identified, the investigator then approached the specific patients and their caregivers at Pumwani Maternity Hospital, after which they were taken to the doctor's consultation room where they were explained the purpose and methods of the study allowing the study participant and their caregiver to provide voluntary informed consent.

Consent was given in written form, on a pre-designed consent form which was availed to the caregiver at this point in time. The consent form provided described the purpose of the study, the study procedure to be followed as well as the potential benefits and risks of participating in the study. The investigator conducted the consent discussion and confirmed that the parent/guardian comprehended the information provided on the consent form. Any pertinent questions regarding the study from the parent/guardian were answered at this point prior to signing the consent form.

Parents/Guardians who accepted to take part in the study were then asked to sign the consent form which was countersigned by the investigator. A copy of the consent form was given to the parents or guardians who consented to the study. Records were also kept regarding reasons for non-participation of eligible participants. Data was then collected from the eligible patients.

**Figure 1: Flowchart Showing Patient Recruitment**



## **Data Collection, Management and Analysis**

### **3.9 Data Collection**

#### **Clinical methods**

After obtaining ethics approval from KNH Ethics Committee and Pumwani Maternity Hospital, continuous medical education (CME) training was held on April 8<sup>th</sup> 2016 at Pumwani Maternity Hospital. This training entailed informing the staff working at New Born Unit (NBU) which included nurses, clinical officers and medical officers about the study and any raises and concerns were answered appropriately. One concern raised was the safety of discontinuing antibiotics after CRP normalization, this concern was answered by sharing with the audience prior studies which have been carried out and demonstrated the safety of using such an approach. Training of research medical assistants was also carried on for a period of two weeks before commencement of data collection. Data collection ran over a period of six months from April 2015 till September 2015, in which 120 subjects were recruited once they fit the inclusion and exclusion criteria and consent was obtained.

We used opaque sealed envelopes which contained randomized block stratification. Once the study was explained to the parent/ guardian and consent was obtained, the envelope was opened and if the letter was marked A the patient was recruited into the control group and if the letter was marked B the patient was recruited into the treatment group.

Patients in the control group were followed up on a daily basis to determine the total duration of antibiotic use, and upon discharge a one week follow up appointment was arranged by telephone to enquire about any readmission or morbidities noticed at



home following the discharge. In the treatment group, a CRP sample was taken at time of admission and every two days until CRP levels were normal, after which a repeat CRP level was done in the next 24 hours to confirm. Patients were then discharged after two normal CRP levels 24 hours apart together with clinical improvement. These patients were also followed up after a period of one week by telephone to enquire about any readmission or morbidities noticed at home during the week.

CRP results were placed in the patient's files for ease of convenience for the clinicians working at the New Born Unit.

## **Laboratory Procedures**

### **Collection and Transport**

1ml of blood was drawn from the patient's peripheral vein using an aseptic technique in intervention group and was placed in a red vacutainer bottle. It was stored at room temperature, in a sealed box and transported to the University of Nairobi Pediatrics and Child health department within the same day. The samples were run on the same day as collection.

### **Methods**

CRP test was run via immunoturbidimetric test, in which the human CRP in patient's specimen, standard and controls reacts with antihuman CRP antibodies in the presence of an enhancer/accelerator buffer. The resulting immune complexes generate a turbidity of the reaction mixture which is proportional to the CRP concentration and can then be measured by turbidimetry.

## **Quality Control**

The analyser equipment was calibrated with the standard calibrators. The internal quality control was set daily every morning, done by running a known quality control sample along with the tests, to confirm the validity of the values of the tests.

Results were calculated by means of a CRP standard curve which was used with each series. Samples for CRP were taken on admission before initiation of antibiotics, then every alternate day and on normalization a repeat sample was taken within 24 hours to confirm. Humastar 600 was used to analyze the CRP sample.

### **3.10 Data Analysis and Management**

Data were entered at the end of each day of collection, from questionnaires into a password protected personal computer. Data was analyzed using SPSS version 19.

Descriptive analysis of demographic characteristics of neonates receiving antibiotic treatment was conducted by calculating mean and standard deviation for continuous variables like age and calculating frequency distribution for categorical data e.g. sex. Cross tabulation was then used to examine the distribution of neonates' demographic and clinical characteristics in the serial CRP and control group. Prior to analysis of the primary outcome the comparability of intervention and control arms following randomization was determined by using Student's T-test for comparison of group means and chi square test for comparing proportions in the two groups. For continuous variables comparison was based on Mann-Whitney U test for variables in which a skewed was detected and for categorical variables Fisher's exact test was used for small cell sizes (cells with expected values of 5 or less).

The primary outcome was the duration of antibiotic treatment in days. The duration of treatment was inspected for normality by calculating residuals and inspecting the

distribution of the residuals using Q-Q plots. Duration of treatment in the two groups (serial CRP and control) was summarized as mean and standard deviation as the data was normally distributed. The duration of antibiotic treatment in the serial CRP group was compared to duration in the control group using the Student's t-test for independent samples. Both intention to treat and per protocol analyses were conducted. Readmission rate in each group was calculated using percentage and compared between the two groups using Fishers Exact Test.

### **3.11 Ethical Considerations**

1. Permission was sought from the Kenyatta National Hospital/University of Nairobi Ethics and Research Review Committee (KNH/UON-ERRC) to analyze the data collected from this study as part of the thesis dissertation.
2. Permission to undertake this study was sought from the ethics committee from Pumwani Maternity Hospital Ethics Board.
3. Risks: no experimental investigations or products were employed in this study. Procedures were undertaken to the study participants and were done with care with minimal acute or long-term risks to the participants.
4. Benefits to participants included health education on neonatal care. No monetary gain was obtained from participating in this study and only those willing were included.
5. Confidentiality- this was maintained at all times, the study participants was given study identification numbers and no personal identification data was recorded.
6. Information sharing- the study findings was presented to the University of Nairobi, Department of Pediatrics and Child Health staff and students and to

Pumwani Maternity Hospital. We also hope to publish these results so as to disseminate the knowledge gained and hope to contribute to the improvement of management of neonatal sepsis.

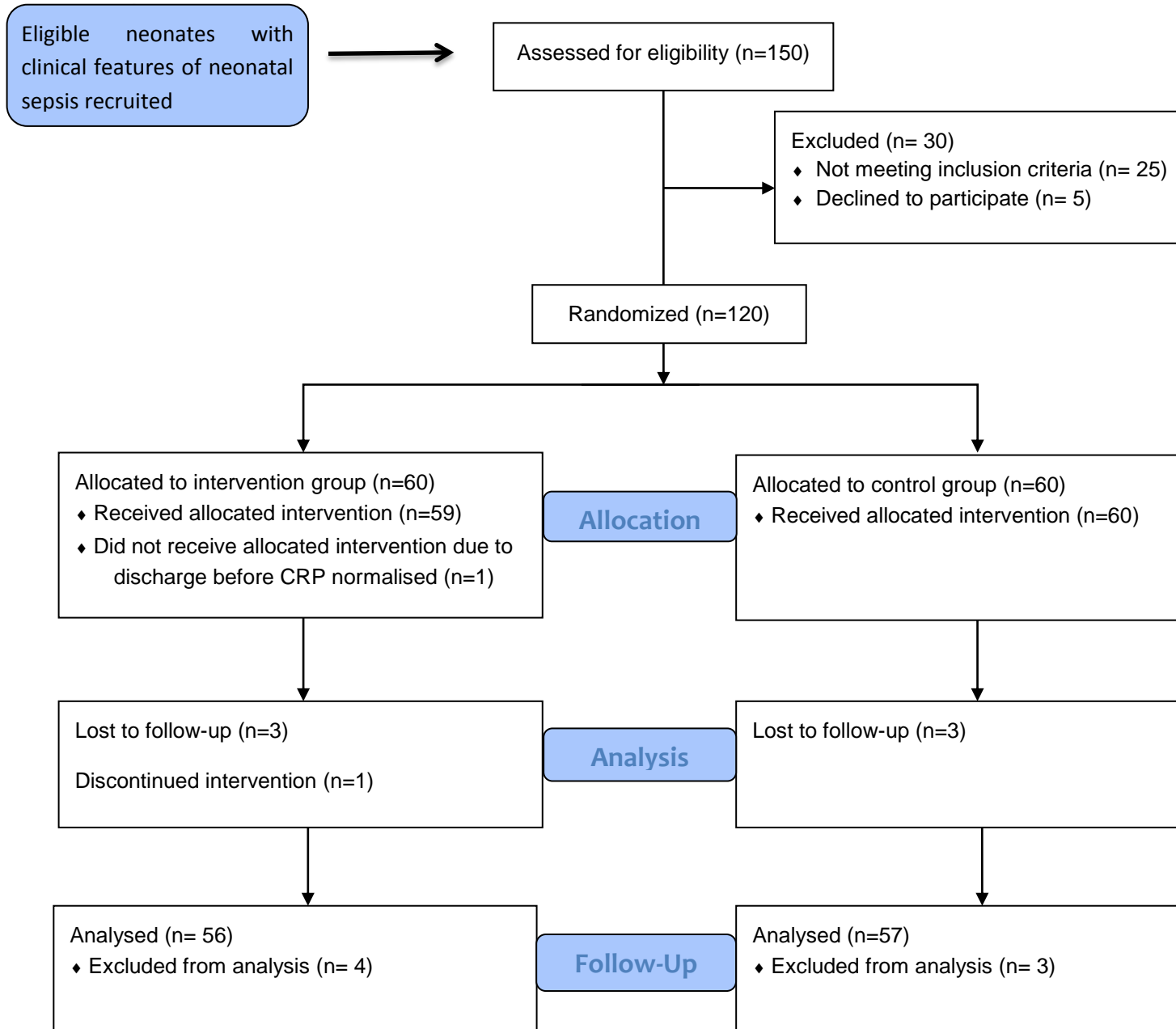
7. Informed consent- the purpose of the study was explained to the caregivers and written informed consent was sought to participate in this study. Confidentiality was observed. Participants were asked to sign a consent form, of which a copy was given to them, and at any time they were allowed to leave from the study. Their participation in the study was voluntary, free of correction and they were free to refuse to participate and were allowed to leave from the study at any given time with no penalties.

## **CHAPTER 4: RESULTS**

### **4.1 Characteristics of Enrolled Patients**

A total of 150 neonates with suspected neonatal sepsis were screened for the study during the data collection period from April till September 2015 at Pumwani Maternity Hospital. These patients were admitted with a diagnosis of suspected neonatal sepsis. 25 neonates were excluded as they did not meet the inclusion criteria. A further 5 neonates were excluded as they and parents/guardians chose not to have their neonates participate after the study was explained to them. A final number of 120 subjects (60 in each arm) were enrolled into the study and randomly assigned to either the control or intervention group. (Figure 2)

**Figure 2: Study Flow Chart**



## Baseline and Clinical Characteristics

**Table 3: Demographics and clinical characteristics of patients admitted with neonatal sepsis**

		<b>Intervention</b>	<b>Control</b>	<b>Chi square</b>	<b>P value</b>
<b>Median age days (IQR)</b>		2 (1-2)	1(1-2)		0.195*
<b>Sex</b>	Male	26(43.3)	40(66.7)	6.6	0.01
	Female	34(56.7)	20(33.3)		
<b>Onset of NNS</b>	EONNS $\infty$	57(95.0)	59(98.3)	2	0.154
	LONNS $\alpha$	2(3.3)	0(0.0)		
<b>Median gestation (IQR)</b>		40 (38-40)	39 (38-40)		0.110*
<b>Mean weight <math>\pm</math> SD</b>		3176.7 $\pm$ 407.7	3120 $\pm$ 497		0.496 $\dagger$
* Mann-Whitney U test; $\dagger$ two sample t-test; $\infty$ Early onset neonatal sepsis; $\alpha$ Late onset neonatal sepsis					

A total of 120 patients were recruited in a sequential manner, 66 male and 54 female patients. The median age was 2 days for intervention group and 1 day in the control group. There were a total of 26 males in the intervention group and 40 males in the control group, whereas there were 34 females in the intervention group and 20 females in the control group and this was statistically different. Majority of the patients had early onset neonatal sepsis, with only 3% of the patients in the intervention group had patients with LONNS while control group had none.

The rest of the parameters were comparable between groups that is gestational age (between 39-40 weeks) and weight (3176-3120 grams).

## 4.2 Maternal and Fetal Predisposing Factors

**Table 4: Maternal and fetal predisposing factors for neonatal sepsis**

		Intervention	Control	Chi square	P value
PROM	Yes	14(23.3)	10(16.7)	0.8	0.386
	No	46(76.7)	49(81.7)		
Fever	Yes	4(6.7)	4(6.7)	0	1
	No	56(93.3)	56(93.3)		
Chorioamnionitis	Yes	7(11.7)	10(16.7)	0.6	0.432
	No	53(88.3)	50(83.3)		
Prolonged labor	Yes	21(35.0)	25(41.7)	0.6	0.453
	No	39(65.0)	35(58.3)		
Low birth weight	Yes	6(10.0)	7(11.7)	0.1	0.793
	No	53(88.3)	53(88.3)		

Maternal predisposing risk factors were comparable in both groups, the highest being prolonged labor (35% in intervention group and 41.7% in control group), followed by premature rupture of membranes (23.3% in intervention group and 16.7% in control group), chorioamnionitis (11.7 % in intervention group and 16.7% in control group) and maternal fever (6.7% in both groups).

In regards to fetal risk factors, there were similar number of patients with low birth weight in both groups at 10% in intervention group and 11.7% in control group, whereas 5% of patients had a low Apgar score in the control group and none in the intervention group.



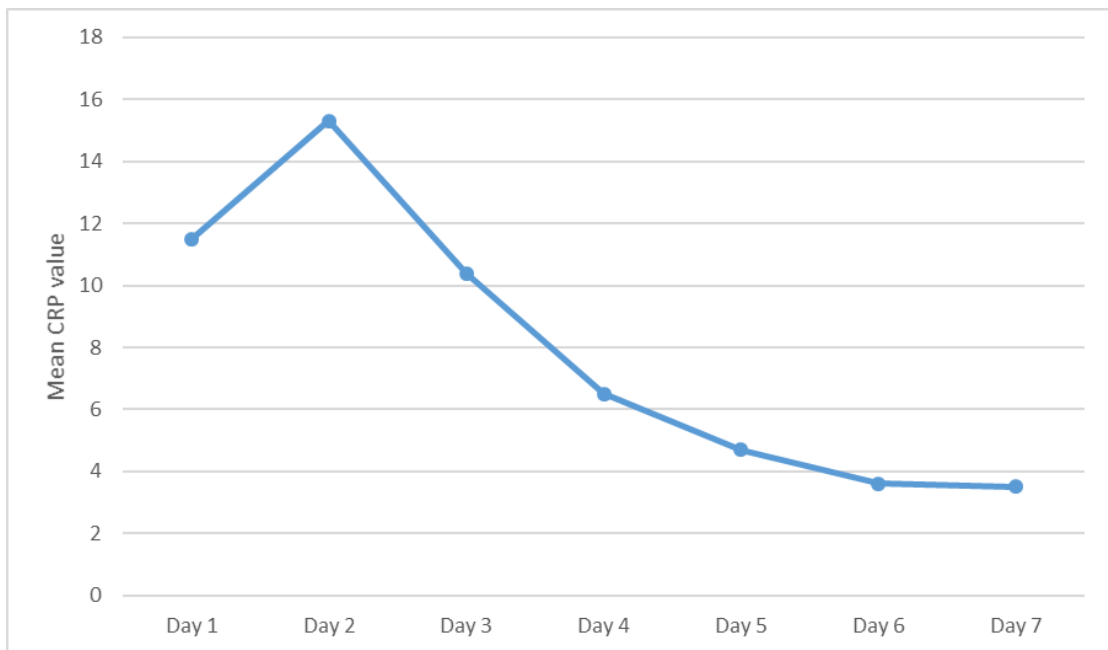
### 4.3 Clinical Features of Study Participants

The most common clinical features in the intervention group was poor feeding (63.3%), fever(51.7%), tachypnea(38.3%), irritability (30%) and lethargy (26.7%) whereas in the control group it was tachypnea (60%), poor feeding (56.7%) , fever (45%) , lethargy (26.7%) and chest retractions (25%). In both groups the commonest clinical features included poor feeding, tachypnea, fever, lethargy and irritability.

**Table 5: Clinical features of patients admitted with neonatal sepsis**

Clinical feature	Intervention	Control	Chi square	P value
Apnea	1(1.7)	0(0.0)	1	0.315
Tachypnea	23(38.3)	36(60.0)	5.6	0.018
Flare	4(6.7)	10(16.7)	2.9	0.088
Cyanosis	0(0.0)	1(1.7)	1	0.315
Retraction	7(11.7)	15(25.0)	3.6	0.059
Tachycardia	2(3.3)	4(6.7)	0.7	0.414
Hypotonia	3(5.0)	2(3.3)	0.2	0.648
Seizures	0(0.0)	1(1.7)	1	0.315
Skin color	9(15.0)	10(16.7)	0.1	0.803
Capillary refill	9(15.0)	10(16.7)	0.1	0.803
Irritability	18(30.0)	10(16.7)	3	0.084
Lethargy	16(26.7)	16(26.7)	0	1
Poor feeding	38(63.3)	34(56.7)	0.6	0.456
Hematochezia	1(1.7)	0(0.0)	1	0.323
Hypothermia	2(3.3)	2(3.3)	0	0.986
Hyperthermia	31(51.7)	27(45.0)	0.5	0.465
Abdominal distension	0(0.0)	1(1.7)	1	0.315
Jaundice	14(23.3)	15(25.0)	0	0.831
Septic spots	15(25.0)	10(16.7)	1.3	0.261

**Figure 3: Chart Showing CRP Levels Trends**



The chart depicts the trends of CRP levels from the patients in the intervention group. 26 out of the sixty patients (43.3%) had normal CRP levels on day one; the mean value of CRP on day one of admission was 11.5. A peak was noted 24 hours later on day 2 after which levels started to decrease most likely due to response to antibiotic treatment.

The lowest value recorded was 2mg/dl and highest level recorded was 120mg/dl.

#### **4.4 Primary Outcome: Duration of Antibiotic Use**

The primary outcome was to compare the duration of antibiotic use between the two groups.

Using the intention to treat analysis, the mean duration of treatment in the intervention group was 6 days and 5.1 days in the control group ( $p=0.041$ ).

**Table 6: Mean duration of antibiotic use**

<b>Mean duration of antibiotic use</b>				
	<b>Intervention</b>	<b>Control</b>	<b>t statistic (df)</b>	<b>P value</b>
<b>Intention to treat (ITT) analysis</b>				
Mean duration in days $\pm$ SD	6.0 $\pm$ 2.7	5.1 $\pm$ 2.3	2.1 (118)	0.041
<b>Per-protocol analysis</b>				
Mean duration in days $\pm$ SD	5.9 $\pm$ 2.5	5.1 $\pm$ 2.3	1.8 (111)	0.08

**4.5 Secondary Outcome: Readmissions within One Week Of Discharge.**

The secondary outcome was to compare the readmission rates between the two groups. 4 patients in the control group were readmitted within one week of discharge; one patient was treated for neonatal meningitis and was admitted for a period of 10 days, whereas the other three patients were readmitted with a diagnosis of neonatal sepsis and were admitted for five and seven days respectively. There were no mortalities reported in any of the readmissions.

There were no readmissions in the intervention group.

**Table 7: Readmissions within one week of discharge**

<b>Readmissions within one week of discharge</b>				
		<b>Intervention</b>	<b>Control</b>	<b>Fishers exact</b>
<b>Intention to treat (ITT) analysis</b>				
Readmission within a week	Yes	0(0.0)	4(6.7)	0.122
	No	59(100)	55(93.2)	
<b>Per-protocol analysis</b>				
Readmission within a week	Yes	0(0.0)	4(7)	0.118
	No	56(100)	53(93)	

#### **4.6 Drug Dosage and Administration**

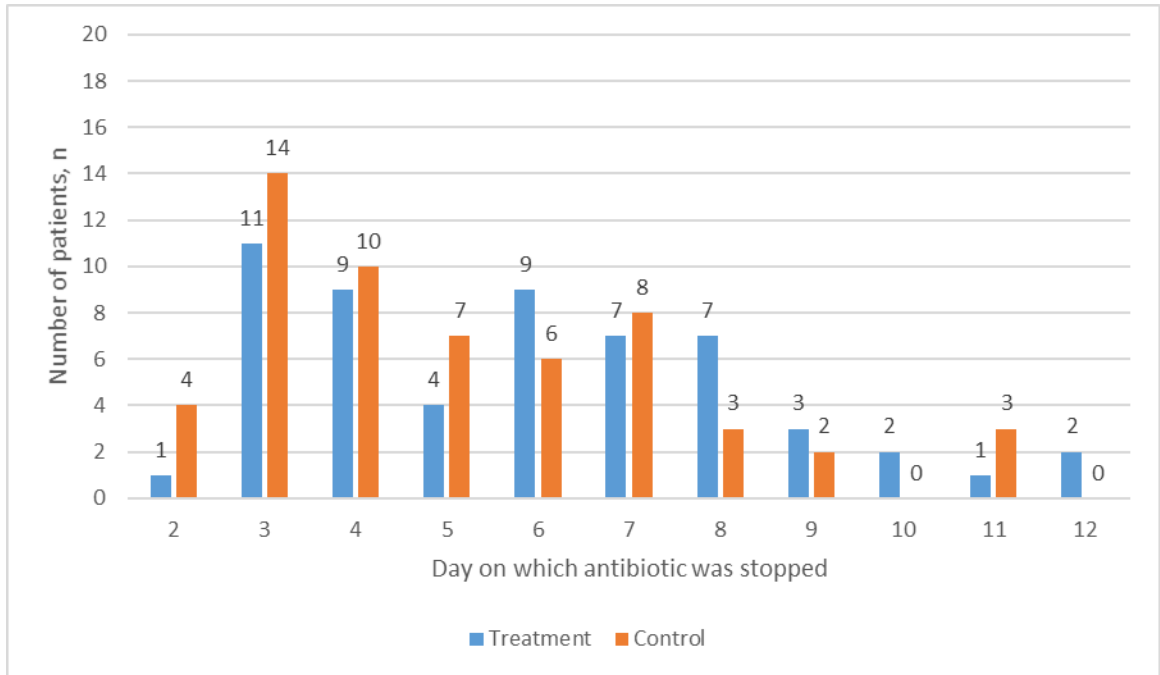
**Table 8: Dosage and Drug Administration**

		<b>Intervention</b>	<b>Control</b>	<b>Chi square</b>	<b>P value</b>
Correct antibiotic dose	Yes	56(93.3)	58(96.7)	0.7	0.402
	No	4(6.7)	2(3.3)		
Correct timing for administration	Yes	60(100.0)	59(98.3)	1	0.315
	No	0(0.0)	1(1.7)		

The table above depicts the number of patients who received the correct antibiotic dose and those patients who received the drugs at the correct time. 93.3% of patients in the intervention group and 96.7% in the control group received the correct

antibiotic dose, and 100% of patients received drugs at the right time in the intervention group as compared to 98.3% in the control group.

**Figure 4: Bar Graph Showing Day on which Antibiotic was Stopped**

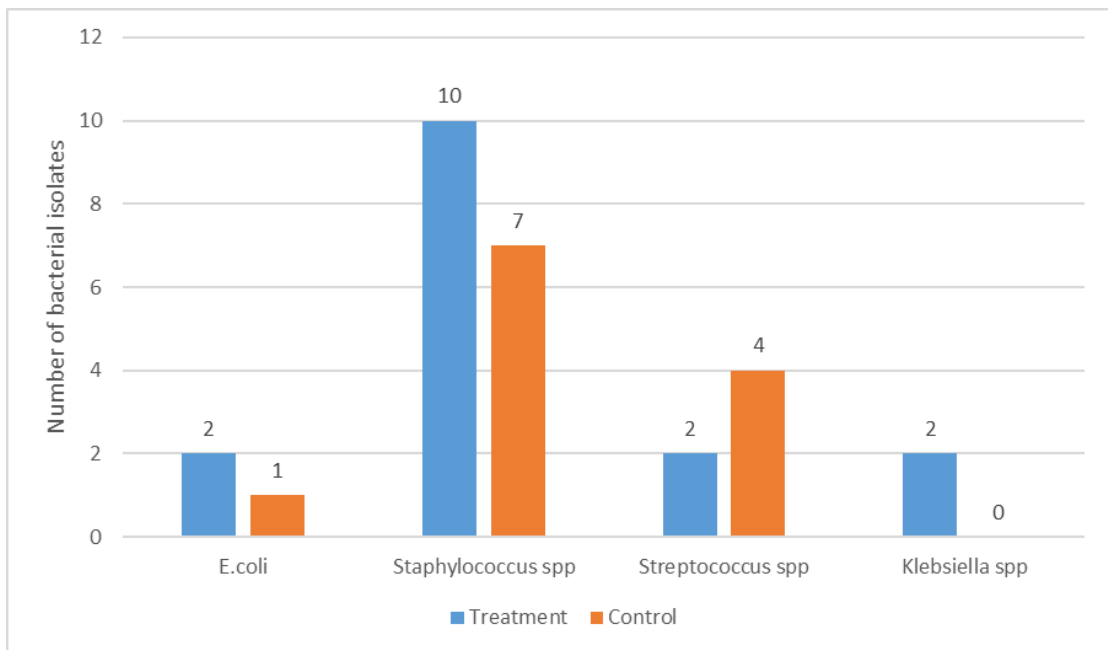


The chart above summarizes the days on which antibiotics were stopped. 61% of patients on the control group were stopped antibiotics and subsequently discharged within 5 days of admission, compared to 45% of patients in the intervention group who were discharged by 5 days.

#### 4.7 Blood Culture Results

Positive blood cultures rates in our patients was 20.8% which is comparable to local studies (23) (25). The most common organism grown was staphylococcus species at 16.7% in the treatment group and 11.7% in the intervention group, the next most common organism was streptococcus at 6.7% in control group and 3.3% in the intervention group. 3.3% of patents in the intervention group had cultures which grew Klebsiella species with no patients in the control group growing Klebsiella species.

**Figure 5: Blood culture results**



## **CHAPTER 5: DISCUSSION, CONCLUSION AND RECOMMENDATIONS**

### **5.1 Discussion**

We sought to determine if using serial CRP would alter the duration of antibiotic usage for patients with suspected neonatal sepsis. In our study we found the mean duration of treatment with antibiotics in the control group using the intention to treat analysis was 5 days compared to 6 days in the intervention group. These results are conflicting with previous studies (8, 9). We found that our control group had markedly shorter duration of treatment, and this could possibly be explained by the large number of patient's turnover at the hospital making it difficult to strictly adhere to the standard protocols especially in a resource limited setting. Patients were being discharged according to clinical improvement in our control group, in some cases patients would be discharged after 48-72 hours, thus leading to shorter duration of antibiotic treatment. In addition to this, CRP levels did not seem to fall as quickly as expected in the intervention group, which was probably attributable to their illness.

Previous studies done in developing countries have shown conflicting results (8, 37), whereby some of the limitations of the study done in Iraq were the lack of a comparison control group and CRP being measured qualitatively not quantitatively, the latter being more specific. Our study had both a control group and measured CRP quantitatively yet our findings were different from the above study as we found there to be less readmissions in the CRP guided arm. However a clinical audit done recently in UK after introduction of new NICE guidelines, which included a repeat CRP value at 18-24-hour, showed that serial CRP led to increased number of investigations and also increased duration of hospital stay and cost of treatment (38) which is similar to our findings in this study.

Other plausible explanations for the difference in duration in antibiotic duration could include that two patients in the intervention group had cultures which grew *Klebsiella* Species with no patients in the control group growing *Klebsiella*. These patients had prolonged duration of stay at 11 and 12 days respectively most likely due to antibiotics insensitivity to chosen treatment and this could explain the prolonged duration of stay.

The secondary objective was to compare the readmission rates between the two groups and the four readmissions were only patients in the control group.

The decision to stop antibiotics in the control group was done based on clinical judgment on how the patient was responding to treatment, whereas in the treatment group this decision was based on clinical judgment as well as CRP level results in which the patient was discharged after two normal results.

Kenyan guidelines on management of neonatal sepsis demonstrate that patients with suspected neonatal sepsis should be started on antibiotics, and should be discontinued at 3 days if blood cultures come back negative. If no cultures were done the duration of treatment should range between five to seven days depending on response to treatment(5). Patients at Pumwani Maternity Hospital were being discharged based on clinical judgment and this could explain why in the control group 32% of patients stopped antibiotics in less than or equal to 3 days, compared to 21% of patients in the treatment group, and could possibly explain why there were more readmissions in the control group.



Strengths of this study includes that it was the first randomized controlled trial in a developing country to determine if there was a difference in treatment of duration of treatment, thus eliminating bias and confounding effects.

## **5.2 Study Limitations**

The following are some of the limitations we experienced:

1. CRP has been shown to be a more accurate marker in LONNS than EONNS and majority of the patients in the study had EONNS.
2. Blood cultures on readmission; we were unable to prove that the reinfection is due to the same organism as in the previous infection or due to a different organism acquired from environment.

## **5.3 Conclusion**

1. The duration of treatment in the intervention group was 6 days and 5 days in the control group.
2. There were four readmissions in the control group and no readmissions in the intervention group.

## **5.4 Recommendations**

We recommend that a larger multi-centre study is carried out to objectively study the use of CRP as an adjunct to clinical acumen in duration of antibiotic use.

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## APPENDICES

### APPENDIX 1: CONSENT FORM

**Research topic:** Role of serial C- reactive protein in determining duration of antibiotic use for neonates with suspected neonatal sepsis: a randomised control trial.

**Investigator:** Dr. Fareena Ahamed, Department of Paediatrics, University of Nairobi.

Emergency contact 0721455990

**Supervisors:** Prof. A.O.Wasuna, Dr Rashmi Kumar Department of Paediatrics, University of Nairobi.

**Ethical approval:** The study has been approved by the Kenyatta National Hospital/University of Nairobi Ethics and Research Review Committee (KNH/UON-ERRC) P.O BOX 20723-00100, Nairobi.Tel.no. 2726300/2716450.Ext 44102.Attached is a copy of the same.

**Introduction:** Neonatal sepsis is a major contributor to neonatal mortality. Early diagnosis and management is critical, however due to the non-specific nature of the signs and symptoms this leads to neonates with suspected neonatal sepsis to be initiated on antibiotics. This leads to overuse of antibiotics where none are required and development of antibiotic resistant strains of organisms. CRP is an infection marker in the blood, its levels rises approximately 6 hours after an infectious trigger and peaks at 12-24 hours after onset of infection. CRP double time is 6 hours and CRP levels fall by up to 50% per day when the acute-phase stimulus resolves, therefore making it a useful inflammatory marker to monitor response to treatment.



**Objectives of the study:** This study has been undertaken with the aim to determine if use of serial CRP can be used to reduce duration of antibiotic use for treatment of suspected neonatal sepsis and to evaluate the clinical outcomes upon discharge after a period of one week in order to monitor for relapse of infection.

**Description of participation:** Your participation will involve;

1. Helping us fill a questionnaire at the time of admission.
2. Full examination of your baby at admission and at subsequent visits.
3. Patients will be categorized by random into two groups. This is like tossing a coin. You have an equal chance of being in each group. A computer will decide at random which group you will be in. You cannot decide which group to be in.

If your baby is in group 1:

They will receive antibiotic treatment for up to five to ten days depending on response to treatment which is the standard recommended practice.

If your baby is in group 2:

They will undergo additional laboratory investigations which involve measuring CRP levels (blood test). This involves taking 0.5ml of blood on admission and on every alternate day.

The results of this lab test will be available to you within one day. Your baby will receive antibiotics until CRP levels are normal and also if your baby has improved. This may mean your baby will receive drugs for 3 days to 10 days depending on the CRP levels.

Whichever group you will be in, your baby will still receive appropriate management which is deemed fit for your baby.

4. Follow up appointment within one week upon discharge home.

**Benefits:** The results of the investigations done will be used for the appropriate management of your baby. The results of this study will be used to manage all babies with similar ailments. The information obtained will be used to improve services in Pumwani Maternity Hospital, to form protocols and may be published in medical journals and/or presented in scientific symposia (both local and international). Benefits to participants will include health education on neonatal care. Benefits of this study include possibility of reducing the number of days of antibiotic exposure by using CRP thus ensuring decreased hospital infections and cost of stay.

**Risks:** Laboratory investigations involve taking a blood sample of 0.5-1ml of blood from your baby. This will cause a mild discomfort to him/her. All precautions will be taken to ensure it's an aseptic procedure and to prevent unnecessary bleeding. Procedures will be undertaken to the study participants and will be done with care with minimal acute or long-term risks to the participants.

**Investigators note:** The purpose of this consent form is to provide you with a detailed knowledge of the study, to enable you to decide whether to participate in this study. Your participation in this research is completely voluntary. If you decide to participate, you may withdraw at any time without consequences or explanation. This will in no way change the treatment plan that your doctors deem is fit for you, or in any other way prejudice either of you. The results of the study will be treated with strictest confidence, your identity will be protected (your name will not be used and you will be identified with a number, only known to me and my immediate assistant).

<b>For any question or clarification, please do not hesitate to contact:</b>
<b>Dr Fareena Ahamed (principal investigator) on 0721455990</b>
<b>Professor Wasuna (Supervisor) on 0722700444</b>
<b>Kenyatta National Hospital/University of Nairobi Ethics and Research Review Committee (KNH/UON ERRC), Kenyatta National Hospital, P.O.Box 20723-00202 Nairobi. Tel: +254-202726300 EXT 44102, 44355.</b>

Consent Form: Participant's Statement:

I \_\_\_\_\_ having received adequate information regarding the study research, risks, benefits hereby AGREE / DISAGREE (Cross out as 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 Signature: \_\_\_\_\_ Date \_\_\_\_\_

I \_\_\_\_\_ declare that I have adequately explained to the above participant, the study procedure, risks, and benefits 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.

Interviewers Signature \_\_\_\_\_ Date \_\_\_\_\_

## **FOMU YA RIDHAA**

**Kichwa cha utafiti:** Wajibu kufuatiliza C-Protini tendaji ili kuamua muda wa matumizi ya madawa ya kupigana na bakteria kwa watoto wachanga wanaopata maambukizi ya damu : Utafiti unaofuata sheria za kudhibiti na randomized.

**Mtafiti:**Dr. FareenaAhamed, Kituo cha Watoto, Chuo kikuu cha Nairobi.Nambari ya dharura pigia 0721455990

**Msimamizi:** Prof. A.O.Wasuna, Dr Rashmi Kumar Kituo cha Watoto, Chuo kikuu cha Nairobi.

**Idhini Maadili:** Utafiti umepitishwa na Kenyatta National Hospital / Chuo Kikuu cha Nairobi Maadili na Kamati ya Utafiti ya Uchunguzi (KNH / UON-ERRC) PO BOX 20723-00100, Nairobi. Numbari ya simu.2726300/2716450.Ext 44102. Ifuatayo ni nakala inayofanana.

**Utangulizi:** Maambukizi ya damu kwa watoto wachanga inachangia pa kuu kwa vifo vya watoto wachanga.Utambuzi wa mapema na usimamizi ni muhimu, hata hivyo kutokana na maumbile hali ambozo si maalum na dalili za magonjwa hii husababisha watoto wachanga wanaodhaniwa kuwa na maambukizi ya damu kwa watoto wachanga kuanzishwa madawa ya kupigana na bakteria. Hii inasababisha matumizi mabaya wa madawa ya kupigana na bakteria ambapo haihitajiki na inaleta viumbe sugu kwa dawa hizi za kupigana na bakteria. Viwango vya CRP zinapanda takriban masaa sita baada maambukizi haya mara inapotokea na kuendelea kuenea kwa masaa 12-24 baada ya chanzo cha maambukizi. CRP mara mbili ni masaa 6 na viwango vya

CRP huanguka kwa hadi 50% kwa siku wakati ambapo ncha kali zinazoamsha zinapungua, hivyo kuifanya kuwa na sehemu ya mwako kwa kufuatilia makubaliano ya matibabu.

**Lengo ya utafiti:** Utafiti huu umechukuliwa kwa lengo la kuamua kama matumizi ya kufuatilia CRP inaweza kutumika kupunguza muda wa matumizi ya dawa ya kupigana na bacteria kwa matibabu ya wanaodhaniwa kuwa na maambukizi ya damu kwa watoto wachanga na kutathmini matokeo ya kliniki baada ya kupewa ruhusa ya kwenda nyumbani baada ya kipindi cha wiki moja ili kufuatilia tukio lingene mpya la maambukizi.

### **Maelezo ya Mshiriki**

Ushiriki wako utahusisha:

1. Kutusaidia kujaza maswali wakati wa uandikishaji.
2. Uchunguzi kamili wakati wa kulazwa na katika ziara za baadae.
3. Wagonjwa watajumuishwa kwa vikundi viwili. Itakuwa kama kurusha sarafu. Nafasi kuingia kwa kikundi yoyote itakuwa sawa. Kichaguo ya kikundi yako itafanyika na tarakilishi bila taratibu. Huwezi chagua ile kikundi una taka.

### Kama mtoto wako atakuwa kwa kikundi cha kwanza

Watapata madawa ya kupigana na bacteria kwa siku tano au kumi, watapata huduma ya kawaida na itategemea kiafya yake vile inaedelea mpaka mtoto wako atakuwa amekuwa heri kiafya.

### Kama mtoto wako atakuwa kwa kikundi cha pili

Atakuwa na vipimo vya ziada za maabara kupima kiwango cha CRP (kipimo ya damu). Hii inahusisha kuchukua mililita 0.5 ya damu wakati wa kulazwa na wakati mwingine kila baada ya siku moja. Matokeo ya vipimo vya maabara itakuwa tayari kwako kwa siku moja. Vipimo hivi vitafanyika mpaka matokeo itakuwa ya kawaida ambayo madawa ya kupigana na bacteria itasimamishwa baada ya siku tatu au kumi kama mtoto wako atakuwa amekuwa heri kiafya.

Kikundi chochote utakuwa, mtoto wako bado atapokea huduma ambayo kwa kawaida anafaa kuipata .

**Faida:** Matokeo ya uchunguzi uliyofanywa itatumika kwa vipasavyo kusimamia mtoto wako. Matokeo ya utafiti huu itatumika kusimamia watoto wote walio na maradhi kama hayo. Habari zilizopatikana zitatumika kuboresha huduma katika Hospitali ya Uzazi ya Pumwani, ili kuunda hati na inaweza kuchapishwa katika majarida ya matibabu na / au iliyotolewa katika makongamano kisayansi (yote ya ndani na kimataifa). Faida kwa washiriki pamoja na elimu ya afya juu ya huduma neonatal. Faida kwa mshiriki itakuwa ni pamoja na masomo ya afya juu ya huduma za watoto wachanga. Faida ya utafiti huu ni pamoja na uwezekano wa kupunguza idadi

ya siku ya kupokea madawa ya kupigana na bakteria kwa kutumia CRP hivyo kuhakikisha kupunguza maambukizi hospitalini na gharama ya kukaa.

**Hadhari:** Uchungu wa maabara unahusisha kuchukua sampuli za damu ya 0.5-1mililita ya damu kutoka mtoto wako. Hii itasababisha usumbufu kidogo kwake. Tahadhari zitachukuliwa kuhakikisha taratibu safi na kuzuia kuvunja damu. Mikakati itachukuliwa kwa washiriki wa utafiti na itafanyika kwa uangalifu kwa hatari ndogo sana au au bila hadhari za muda mrefu kwa washiriki.

**Tamko la mtafiti:**

Madhumuni ya fomu hii ya idhini ni kukupa taarifa ya kina ya utafiti, ili kuwawezesha wewe kuamua kama utashiriki katika utafiti huu. Kushiriki kwako katika utafiti huu ni kwa hiari kabisa.

Kama utaamua kushiriki, unaweza kuondoa wakati wowote bila adhabu au maelezo. Hii kwa vyovyote haitabadilicha mpango wa tiba ambao madaktari wako wanadhani ni nzuri kwa ajili yako, au katika njia nyingine yoyote kuleta chuki kwa mmoja wenu. Matokeo ya utafiti itaangaliwa kwa usiri wa juu, utambulisho wako utatalindwa (jina lako halitatumika na utatambuliwa na nambari, inayojulikana tu na mimi na msaidizi wangu).

**Kwa ajili ya swali lolote au ufafanuzi, tafadhali usisite kuwasiliana na mimi kwa 0721455990, au msimamizi wangu Profesa Wasuna kwa 0722700444 au wasiliana na mwenyekiti wa Maadili kamati, Hospitali ya Taifa ya Kenyatta, SLP 20723-00202 Nairobi Tel 254-202726300**

Fomu ya idhini: Tamko la muhisika:

Mimi \_\_\_\_\_ baada ya kupokea taarifa za kutosha kuhusu utafiti utafiti, hatari, faida hvyo na KUBALIANA / KUTOKUBALIANA (weka alama iliyofaa) kushiriki katika utafiti na mtoto wangu. Mimi ninaelewa kwamba ushiriki wetu ni kwa hiari na kwamba mimi niko huru kuondoa wakati wowote. Nimepewa fursa ya kutosha kuuliza maswali na kutafuta ufafanuzi juu ya utafiti na wamejibu kuridhisha.

Sahihi ya mazazi: \_\_\_\_\_ Tarehe \_\_\_\_\_

Mimi \_\_\_\_\_ natangaza kwamba nimeeleza vya kutosha kwa mshiriki hapo juu, utaratibu wa utafiti, hatari, na faida na alizopewa kwake wakati wa kuuliza maswali na kutafuta ufafanuzi kuhusu utafiti. Nimejibu maswali yote ilioulizwa kwa kadri ya uwezo wangu.

Sahihi la mfanyikazi \_\_\_\_\_ Tarehe \_\_\_\_\_



## APPENDIX 2: QUESTIONNAIRE/ DATA COLLECTION FORM

Date.....Serial number.....

Hospital

Number.....

### **SECTION A. DEMOGRAPHIC CHARECTERESTICS**

1. Age at admission.....
2. Male.....  
Female.....
3. Gestational age.....
4. EONNS.....  
LONNS.....
5. Weight.....
6. Feeding method.....

### **SECTION B: MATERNAL/ FETAL PREDISPOSING FACTORS**

Feature	Yes	No
Maternal prolonged rupture of membranes $\geq$ 18 hours		
Intrapartum maternal fever > 38 degrees		
Chorioamnionitis		
Prolonged labour $\geq$ 18 hours		
Low APGAR ( < 5 at 1 min)		
Low birth weight ( $\leq$ 2500 gms)		

**SECTION C: CLINICAL SIGNS AND SYMPTOMS**

CLINICAL FEATURE	TICK IF PRESENT	CLINICAL FEATURE	TICK IF PRESENT
❖ Apnoea ❖ Nasal flare ❖ Chest retraction		❖ Tachypnoea ❖ Cyanosis	
❖ Bradycardia		❖ Tachycardia	
❖ Hypotonia		❖ Seizures	
❖ Poor skin colour		❖ Capillary refill > 3 seconds	
❖ Irritability		❖ Lethargy	
❖ Poor feeding		❖ Hematochezia	
❖ Hypothermia		❖ Hyperthermia	
❖ Bulging fontanelle		❖ Tense abdominal distension	
❖ Abnormal posture		❖ Abnormal muscle tone	
❖ Neck retraction		❖ Neck stiffness	

**SECTION D: LAB RESULTS**

1. CRP done (a) yes (b) no ( if no proceed to section E)
2. No. of serial CRP done.....
3. Highest value of CRP .....
4. CRP stopped on normalization? (a) yes (b) no
5. If yes: which day of treatment? .....
6. If no:

- i. Reasons? Lack of clinical improvement? .....
- .....
- ii. How many extra days of antibiotic done after CRP normalization?  
.....

**SECTION D: DRUG ADMINISTRATION**

- 1. Was the correct dose of antibiotics given? (a) yes (b) no
- 2. Was it administered at correct time?

X penicillin:

Gentamycin:

Ceftriaxone:

Amikacin:

Others:

**SECTION E: CLINICAL OUTCOMES**

- 1. Was the patient readmitted within one week of discharge? (a) yes (b) no  
If yes proceed to question 2, if no proceed to question 5
- 2. If yes: what was admission diagnosis?
- 3. How many days of admission?
- 4. Outcome of readmission?
- 5. Any other morbidity/complications noticed at home?

### **APPENDIX 3: CRP ESTIMATION**

**Overview:** CRP is an acute phase reactant, synthesized in the liver. Inflammatory processes, bacterial infections, polytrauma and other diseases including neonatal sepsis cause an increase in CRP concentration in serum. CRP levels rise approximately 6 hours after an infectious trigger and peak at 12-24 hours after onset of infection. It has a half-life of 19 hours indicating extremely rapid turnover compared with the majority of plasma proteins. CRP double time is 6 hours and CRP levels fall by up to 50% per day when the acute-phase stimulus resolves, therefore making it a useful inflammatory marker to monitor response to treatment.

**Specimen:** Serum (Red vacutainer). Amount required 0.5-1ml of blood.

**Procedure:** Samples for CRP will be taken on admission before initiation of antibiotics, then every alternate day and on normalization a repeat sample will be taken within 24 hours to confirm.

**Method:**

Humastar 600 will be used to analyze the CRP samples. Human CRP in patient specimen, standard or control reacts with antihuman CRP antibodies in the presence of an enhancer/accelerator buffer. The resulting immune complexes generate a turbidity of the reaction mixture which is proportional to the CRP concentration and can be measured by turbidimetry. Results will be calculated by means of a CRP standard curve which is to be used with each series.

**Quality control:**

The internal quality control is set daily every morning, done by running a known quality control sample along with the tests, to confirm the validity of the values of the tests.

**Performance characteristics:**

Linearity: 3-160 mg/L

Analytical sensitivity: 3mg/L

Functional sensitivity: 5mg/L

**Results:**

Results will be obtained and available to the clinician within twenty four hours of sample being drawn. Once CRP levels normalize the levels will be repeated within 24 hours and if still normal, antibiotics will then be stopped in the intervention group in concordance with clinical improvement.





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8<sup>th</sup> April, 2015

Dr. Fareena Ahamed  
Dept. of Pediatrics and Child Health  
School of Medicine  
University of Nairobi

Dear Dr. Fareena

**Research Proposal: Role of Serial C-Reactive Protein in Determining Duration of Antibiotic Use for Neonates with Suspected Neonatal Sepsis: A Randomized Control Trial (P11/01/2015)**

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above proposal. The approval periods are 8<sup>th</sup> April 2015 to 7<sup>th</sup> April 2016.

This approval is subject to compliance with the following requirements:

- a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
- b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH/UoN ERC before implementation.
- c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH/UoN ERC within 72 hours of notification.
- d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
- e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
- f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
- g) Submission of an *executive summary* report within 90 days upon completion of the study  
This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

For more details consult the KNH/UoN ERC website [www.erc.uonbi.ac.ke](http://www.erc.uonbi.ac.ke)

Yours sincerely,



**PROF. M. L. CHINDIA**  
**SECRETARY, KNH/UON-ERC**

c.c. The Principal, College of Health Sciences, UoN  
The Deputy Director CS, KNH  
The Chair, KNH/UoN-ERC  
The Dean, School of Medicine  
The Chair, Dept. of Pediatrics and Child Health  
Supervisors: Prof. A.O. Wasunna, Dr. Rashmir Kumar



