PREVALENCE OF EARLY ONSET SEPSIS AMONG TERM NEWBORNS IN THE POST NATAL WARDS OF KENYATTA NATIONAL HOSPITAL

A dissertation submitted in part fulfillment for the degree of Master of Medicine (MMed) in Paediatrics and Child Health

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DECLARATION

I hereby certify that this is my original work and that it has not been submitted in any other university or forum.

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DEDICATION

I dedicate this thesis to each member of my loving family who have been a great pillar of strength and source of inspiration and to whom I am forever grateful.

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ABBREVIATIONS

C/S……Caesarian Section

CONS……..Coagulase Negative Staphylococci

CRP……..C - reactive protein

EOS ……..Early Onset Sepsis

E coli…….Escherichia coli

GBS……. .Group B Streptococci

GFA……. .Ground Floor A

GFB……. .Ground Floor B

IAP……. Intrapartum Antibiotic Prophylaxis

KDHS ……. .Kenya Demographic and Health Survey

KNH……..Kenyatta National Hospital

MCH……..Maternal and Child Health

MDG……..Millennium development goal

PMN…….....Polymorphonuclear

PROM…….Premature Rupture of Membranes

ROM……...Rupture of Membranes

SVD…….Spontaneous Vertex Delivery

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ABSTRACT

Background: Neonatal sepsis ranks third as a leading cause of infant mortality worldwide. In Kenya it accounts for 60% of the current neonatal mortality rate which stands at 31 deaths per 1000 live births. Despite considerable burden of disease, few data exist on precise incidence and aetiology of early onset neonatal sepsis in sub-Saharan Africa. This study addresses this gap.

Objectives: To determine the proportion of term newborns at risk of neonatal sepsis using two clinical screening tools, prevalence and aetiology of early-onset sepsis in at risk term newborns in the post natal wards of Kenyatta National Hospital (KNH).

Methods: All apparently well term newborns aged 0 – 72 hours old and their mothers at the KNH post natal wards formed the baseline population. Structured questionnaires were administered to consenting mothers in the post natal wards that assessed presence of maternal risk factors and presence of neonatal clinical features suggestive of sepsis. Newborns at risk of sepsis were further evaluated for C-reactive protein (CRP) levels, blood culture and sensitivity and classified as proven (positive blood culture), probable (positive CRP or ≥ 1 clinical feature of sepsis) and no sepsis. Newborns were followed for 72 hours. Those discharged during this time period were followed using telephone interviews. Empirical treatment (Crystalline penicillin and Gentamicin) was started for all babies while awaiting results. Those with probable sepsis continued treatment up to five days depending on clinical assessment on day three and proven sepsis group for seven days. Univariate analysis was used for categorical variables and descriptive statistics for continuous or discrete variables. Bivariate analysis was used to investigate associations between neonatal sepsis and socio demographic variables.

Results: Between October 2012 and February 2013, 449 term newborns in the post natal wards were screened for sepsis risk and 139 (31%) found to be at risk. Of the 139 at risk, proven sepsis prevalence was 12% while 58% had probable sepsis. Coagulase negative Staphylococcus (CONS) accounted for 43.5% of isolates. Gram negative bacteria, Escherichia coli, Enterobacter spp. and Proteus spp. accounted for 21% of the isolates.

Conclusion: There is a significant number of well appearing term newborns with sepsis in the post natal wards and as such require routine screening prior to discharge.

CLINICAL DEFINITIONS

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

Term newborns are babies born after 37 completed weeks of gestation.

Low birth weight refers to a weight less than 2,500 grams at birth.

At-risk newborn are those whose mothers have perinatal risk factors (see table 1) or those with 1 or more clinical feature suggestive of sepsis (see table 2).

Tachypnoea is a respiratory rate ≥ 60 breaths/minute.

1. INTRODUCTION

1.1 Background

Early onset sepsis (EOS) is defined as bloodstream infection at less than or equal to 72 hours of age (1). It is usually due to vertical transmission from contaminated amniotic fluid or during vaginal delivery from bacteria colonizing or infecting the mother's lower genital tract (2). Group B Streptococci (GBS) and Escherichia coli continue to account for approximately two-thirds of early-onset infection (3-5)

Neonatal sepsis remains a major contributor to infant morbidity and mortality. Neonatal mortality accounts for 41% of all under-five mortality (6). There has been greater progress in reducing post-neonatal causes of under-five mortality and therefore the proportionate contribution of neonatal mortality to under-five mortality has increased (from 37% in 2000-03 to 41% in 2008) with sepsis being tthe third most common contributor (6% of the deaths) (7). In Kenya, the recent Kenya Demographic and Health Survey (KDHS) report revealed an under-five mortality rate of 74 deaths per 1000 live births, infant mortality rate of 52 deaths per 1000 live births, post neonatal mortality rate of 21 deaths per 1000 live births and a neonatal mortality rate of 31deaths per 1000 live births. Thus, in Kenya, 70% of the deaths in infants occur in the first year of life, 60% in the first month of life (8). In a study done in Kilifi, Kenya, over a 19 year period (1990 - 2008) showed that most deaths occurred during the first week of life, with 70% of all deaths occurring within the first forty-eight hours of life. Overall death among the very young neonates (< 7days old) was significantly higher (30.5%) compared to the rest of the neonatal period (12.1%) (9)

Various countries have adapted several measures to achieve the fourth millennium development goal of reducing child mortality rate by two thirds by 2015. Focus is placed on the continuum of care from pre-pregnancy states through to pregnancy, child birth, postnatal period and early childhood (10).

Maternal and infant characteristics as well as infant laboratory values have been found useful in identification of infants at high risk of infection. This approach results in evaluation of approximately 15% of well appearing term infants in addition to late preterm and nearly all preterm infants. Development of multivariate screening tools will lead to early identification of newborns at high risk and allow for more limited newborn antibiotic exposures (11).

2. LITERATURE REVIEW

A retrospective study done in a large maternity center in Boston by Mukhopadhyay et al revealed that 1062 (14.7%) of 7,226 well appearing infants, more or equal to 35 weeks gestation were evaluated for early onset sepsis and that half of these received empiric treatment. Of these, only three cases of blood culture-proven infection were identified. The study concluded that improved approaches were needed to identify asymptomatic infants at risk to decrease unneccesary evaluations and limit antibiotic exposure (12).

In Mwanza,Tanzania, a study done to assess predictors of positive blood culture and deaths among neonates with suspected neonatal sepsis in a tertiary hospital revealed a sepsis prevalence rate of 39%. Convulsions, lethargy, inability to feed, cyanosis, prolonged rupture of membranes (PROM) and meconium stained liquor were significant predictors of positive blood culture in both early and late onset neonatal sepsis (13).

The Young Infants Clinical Signs Study Group assessed clinical signs that predict severe illness in children under age 2 months in several centers. Seven signs were identified as a good predictors of severe illness in children less than two months; history of difficulty feeding, history of convulsions, lethargy, tachypnoea of 60 breaths per minute or more, severe chest indrawing, temperature of 37·5°C or more or below 35·5°C)(14).

In the longest running, single-center longitudinal database of neonatal sepsis (1928-2003), there has been notable change in the demographics, pathogens, and outcome associated with neonatal sepsis. The predominant cultured organism was group B streptococcus (GBS), followed by Escherichia coli, staphylococcus species, and aerobic gram-negative rods other than E coli. However, the overall percentage of sepsis caused by GBS and E coli has been noted to decrease. Episodes of sepsis caused by coagulase negative staphylococci (CONS), Staphylococcus aureus, and Candida species were noted to increase in study period 1999-2003 compared with the previous period (1994-1998) (3).

2.1 Diagnosis of Neonatal Sepsis

The criteria for diagnosis of early onset neonatal sepsis include clinical presentation, positive blood cultures and non-specific laboratory tests.

2.1.1 Clinical Diagnosis

Each neonate should be assessed for maternal and neonatal risk factors (see table 1 and 2 below).

Table A Perinatal risk factors for early onset sepsis
Intrapartum maternal fever ≥38ºC (100.4ºF)
Multiple vaginal examinations (> 4)
Prolonged rupture of membranes (> 18 hours)
Foul smelling liquour
Chorioamnionitis
Maternal GBS colonization
Low birth weight (< 2500g)

The risk of proven sepsis increases 10 fold when membranes are ruptured beyond 18 hours (15). A multi-center study done by Puopolo et al estimated the probability of neonatal early onset infection based on maternal risk factors. Postterm delivery, maternal fever,and prolonged ROM were strong individual predictors of infection (16).

Positive GBS status, compared with either negative status or negative/unknown status, was not significantly associated with increased risk of EOS .

Escobar et al studied a cohort of 2785 infants with a birth weight of 2000 g evaluated for EOS during a period (1995–1996) in which intrapartum antibiotic prophylaxis (IAP) was administered by using a risk-based strategy (17).That study identified maternal fever, intrapartum antibiotic treatment, and infant clinical status as the most important factors for predicting culture proven infection among an at-risk cohort.

The clinical features suggestive of sepsis are shown in Table 2.

Table B Clinical features suggestive of early onset sepsis
Refusal to breastfeed
Lethargy
Hypothermia (axillary temperature < 35.5^{o}c)
Hyperthermia (axillary temperature > 37.5 ^{o}c)
Tachypnoea
Severe chest wall in-drawing
Convulsions

2.1.2 Laboratory diagnosis

Laboratory diagnosis of neonatal sepsis is categorized into:

i. Direct method

ii. Indirect method

2.1.2.1 Direct method

This involves isolation of microorganisms from blood, CSF, urine, pleural fluid, pus gastric aspirates, tracheal aspirates and other sites.

Blood culture remains the gold standard for diagnosis of neonatal sepsis. Sensitivity of one blood culture to detect bacteremia is approximately 90%. However, there is a significant time lag before blood culture results are available, and blood cultures may lead to false negative results in about 10 percent of septic cases. As a result, clinical assessment and laboratory tests are used to identify neonates at significant risk for sepsis so that empiric antibiotic treatment may be initiated while awaiting blood culture results.

Culture of urine, gastric contents, and body surfaces is not recommended (2). The yield for positive urine cultures in the diagnosis of EOS is low (15)**.**

2.1.2.2 Indirect method

There are a variety of other laboratory tests that are surrogate measures of sepsis. These include complete blood count, CRP and a micro-Erythrocyte Sedimentation Rate (ESR)

A Complete Blood Count if obtained within the first 24 hours may be helpful in diagnosis of EOS. Low (<5000/microL) total white blood cell count (WBC); absolute (<1000 granulocytes/polymorphonuclear cells (PMN)/microL) or relative (<5000 PMN/microL) neutropenia; or a predominance of immature PMN's relative to the total PMN count (immature/total ratio 0.2 or above) were associated with blood-culture-proven early-onset disease. The limitation of these tests is that the wide range of normal levels reduces their positive predictive value, especially in asymptomatic patients (18).

CRP, an acute phase reactant, increases in inflammatory conditions, including sepsis. Serial CRP has been found useful in diagnosis of early neonatal sepsis. It can be positive as early as six hours post infection. A study done in Kenya by Kumar et al in 2006 showed serum CRP was an accurate indicator of neonatal sepsis with high sensitivity (88.9%), specificity (82.5%) and negative predictive value (96.6%), at the standard cut-off of 5mg/dl (19). To note is that CRP may also be elevated in some noninfectious conditions such as fetal distress, stressful delivery, perinatal asphyxia, meconium aspiration, and intraventricular hemorrhage (20).

The micro-ESR may be elevated with sepsis and a fall of more than 15 mm during first hour indicates infection.

3. STUDY JUSTIFICATION

Neonatal sepsis is the third most common contributor to neonatal deaths worldwide. Danger lies in the non-recognition of early onset sepsis. Signs and symptoms of sepsis tend to be subtle and nonspecific. Therefore, identification of risk factors and any deviation from an infant's usual pattern of activity or feeding should be regarded as a possible indication of systemic bacterial infection. Ability to identify newborns at high risk of sepsis will allow for judicious use of empiric antibiotics and hence limit antibiotic exposure to those who don't need antibiotics.

Despite a considerable burden of disease, few data exist on the precise incidence and aetiology of early onset neonatal bacterial sepsis in sub-Saharan Africa, largely because of a lack of reliable microbiological facilities.

Telephone interviews with mothers after hospital discharge have been found to significantly reduce mortality as a result of early identification on danger signs and improved health seeking behavior by these mothers. Most deaths in the neonatal period occur within the first week of life, more so in the first forty eight hours.

This study aims to assess the proportion of term newborns at risk of early onset sepsis in the postnatal wards and among those, determine prevalence of early onset sepsis and aetiology with 72-hour follow up thereafter. With this information, we can inform the current treatment protocol of neonates at the Kenyatta National Hospital.

4. OBJECTIVES

Study question

What is the proportion of sepsis in term newborns in the post natal wards of KNH and what are the causes?

4.1 Primary objectives

1. To determine the proportion of term newborns at risk of neonatal sepsis using two standardized clinical screening tools
2. To describe the prevalence and aetiology of early onset sepsis in at-risk term newborns at KNH

5. METHODOLOGY

5.1 Study Design

Hospital based descriptive cross sectional study

5.2 Study Area

Term newborns were recruited from three postnatal wards at the Kenyatta National Hospital (KNH); namely, Ground Floor wards A and B and ward 1 A. Each ward has an average daily turnover of 10-15 newborns per day who room-in with their mothers.

5.3 Study Population

All term newborns aged 0 – 72 hours old at the KNH post natal wards formed the baseline population and were to include those born within or without the hospital. None of recruited newborns had congenital abnormalities.

5.3.1 Inclusion Criteria

All mother-baby pairs in the postnatal wards who accepted participation in the study were recruited.

5.3.2 Exclusion Criteria

1. Premature infants (gestational age < 37 completed weeks).

5.4 Case Definition

1. Proven sepsis defined those whose blood culture yielded pathogenic bacteria.
2. Probable sepsis defined those whose clinical and /or CRP findings were consistent with this diagnosis but cultures were negative.
3. No sepsis defined those with no clinical or CRP findings attributable to sepsis.

5.5 Sample Size Calculation

This was done using Fischer's formula

$$n = \frac{Z^2 p (1-p)}{e^2}$$

Z corresponds to the 95% confidence level (1.96)

E is the margin of error 5% (0.05)

P: Prevalence of early onset neonatal sepsis in Muhimbili National Hospital, Tanzania (22%) [22]

Therefore,

n = 263 mother-baby pairs in the postnatal wards

5.6 Study Procedures

Study Timetable

This study was conducted between October 2012 and February 2013.

Patient Recruitment

Consecutive mother-baby pairs in the postnatal wards were approached for participation in the study and grouped as follows:

1. Term infants with no maternal risk factors and no feature(s) suggestive of neonatal sepsis (group one)
2. Term infants whose mothers had maternal risk factors of neonatal sepsis +/- one or more features of neonatal sepsis in the baby (group two). These were further evaluated.

Consent

Consent was sought from all the participants after clear explanation of purpose of the study and involved procedures. A witness was required to sign on behalf of participants who were unable to read the forms themselves after the explanation.

Study tools

Mothers were interviewed and clinic cards reviewed (where available) to determine presence of risk factors for early neonatal sepsis. This was conducted from Monday – Friday, 8am-4pm. The information was documented in a structured standardized questionnaire (appendix 1). The questionnaire sought biographic details of the participants, antenatal history, perinatal history and postnatal history all in a bid to seek newborns at risk of sepsis.

The newborns had their baseline characteristics and examination findings recorded in the newborn assessment form; (appendix 2). The first examination was done within 12 hours of delivery and continued daily for three days. Babies who did not have any maternal or neonatal features of possible sepsis were not evaluated further.

The newborn baseline characteristics included gestation (in weeks) at delivery, mode of delivery, Apgar score at 5 minutes and sex.

5.6.1 Diagnostic procedures

Sample collection

1.5 mls of blood was collected for blood culture and CRP at initial evaluation. These procedures are outlined below.

Blood culture

A sample was collected only from the recruited newborns with risk factors for sepsis. This was done prior to antibiotic administration.

- ***Skin preparation:*** The identified venepuncture site was disinfected with 10% povidone iodine and left to dry. Subsequently, the area was wiped with 70% alcohol and punctured using a size 21 gauge hypodermic needle attached to a 5cc syringe.

- ***Collection***: 1 ml of blood was drawn to allow for reliable detection of bacteremia. It was collected into a hemoline diphasic performance blood culture bottle. The bottle contains two culture media: broth enriched with growth factors and agar covering one side of the bottle. Time lag between sample collection and introduction into the media was 3-4 hours.

- The blood was incubated at 35-37 ^{o}C in upright position and the bottles examined daily for 7 days.

- ***Storage:*** Samples collected were delivered to the lab within 4 hours therefore incubation was not required (where a delay occurs beyond 4 hours, it warrants incubation at 37^{0}c)

- ***Culture Method:*** The blood was cultured in 25 ml of brain heart infusion broth containing para-aminobenzoic acid and incubated in 5% $C0_2$ at 37^{o}C in an automated incubator. Blood cultures were subcultured after a positive signal from the incubator onto blood,

chocolate and MacConkey agar plates. An optochin disc was placed onto the blood agar plate to detect any pneumococci. The blood cultures were subsequently observed for a further 7 days for signs of bacterial growth.

- ***Interpretation of results:*** On agar – presence of colonies or production of gas; In broth – appearance of turbidity, a deposit or hemolysis

CRP levels

0.5 ml of blood was used for analysis and collected in the plain red vaccutainer. The samples were run daily within 4 hours of collection

Method: The test was by latex agglutination; the reagent contains particles coated with specific anti-human CRP antibodies and agglutinates in the presence of CRP in the patient's serum.

Interpretation:

- Positive result: presence of agglutination; indicates a CRP level of ≥ 6 mg/l
- Negative result: no agglutination; level < 6 mg/l

Further analysis: The last dilution step with visible agglutination is noted and that titer read. A semi-quantitative value can then be obtained by multiplying the titer value with the conversion factor 6. Results were to be charted in mg/l, however, due to lack of micropipettes in the lab, the semi-quantitative values could not be obtained. Therefore, patients were said to either have a positive or negative CRP.

5.7 Follow up

These children were followed up till 72 hours post delivery and treatment instituted as follows:

1. **Proven sepsis**

   Those defined as proven sepsis were put on Crystalline Penicillin and Gentamycin for 10days.

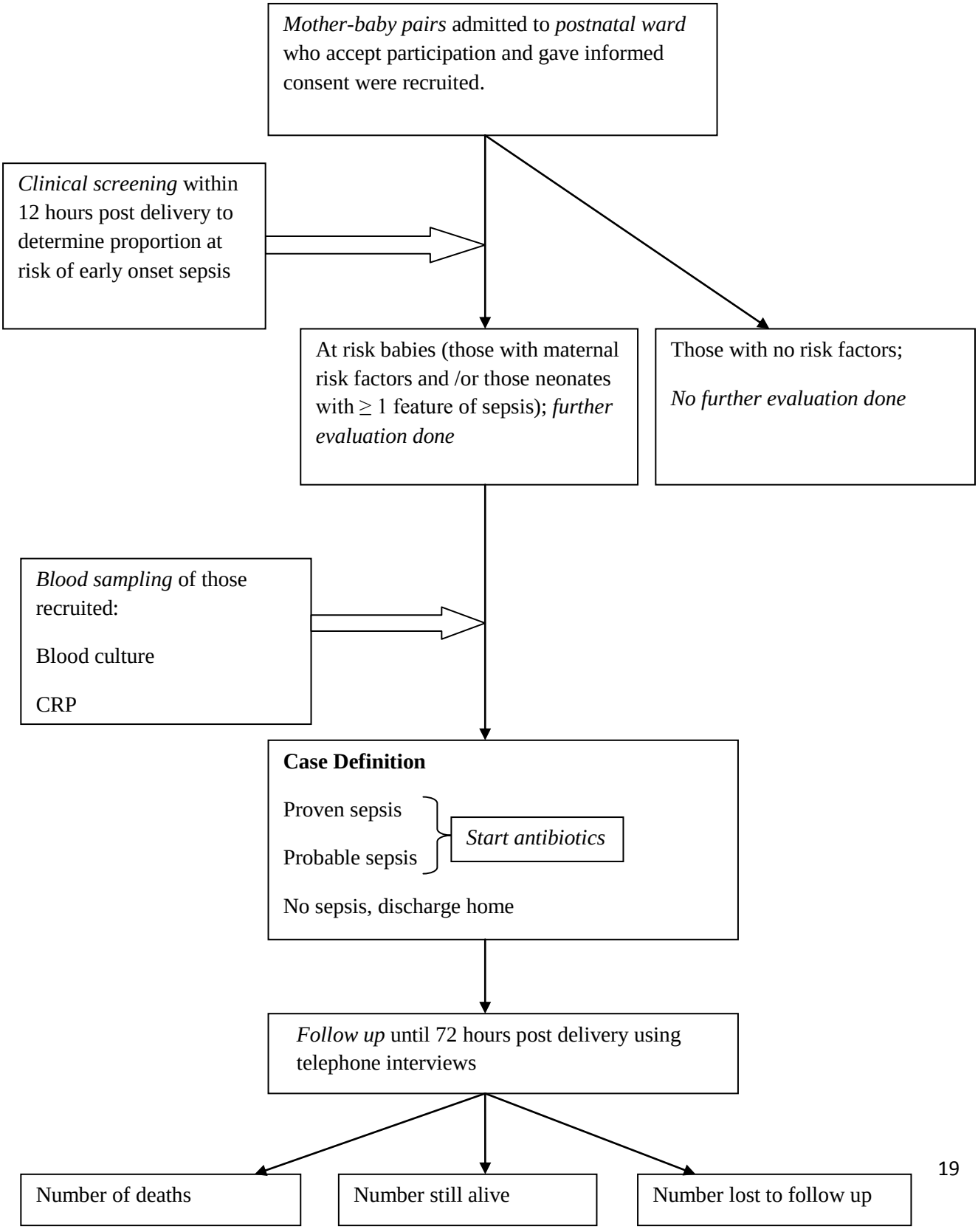
2. **Probable sepsis**

   Those defined as probable sepsis were started on Crystalline Penicillin and Gentamycin empirically and clinical progress assessed over 48hours. If blood cultures were negative, empiric antibiotic therapy was discontinued in the well-appearing neonate after 48 hours. If sick looking, oral treatment (amoxil) was continued for seven days . Follow up was done up to 72 hours to ascertain the wellbeing of the neonate.

3. **No sepsis**

   Those defined as no sepsis were observed for at least 24 hours. If they remained clinically stable, they were discharged home. On discharge, follow up continued to up to 72 hours post-delivery via telephone interviews.

Summary of methodology



Study Limitations

Several limitations were faced in this study.

1. Inadequate funds that led to incomplete septic screening in these babies (No full blood counts, immature: total polymorphonuclear cell ratios were done). This would have worked to strengthen my diagnostic criteria for sepsis.
2. The immunology lab lacked equipment to perform a quantitative CRP analysis. Actual CRP values would have enabled better distinction between the three groups.

5.8 Ethical Considerations in the Research

Ethical clearance was obtained from the Department of Paediatrics & Child Health KNH and the Ethics and Research Committee KNH. Written and signed consents were obtained from each mother after a detailed explanation of the study being undertaken.

Risks

In order to determine presence of infection, a blood sample from the baby was required. This was a cause of pain and discomfort to the babies. All precautions were taken against any unnecessary bleeding during sample collection.

Benefits

The study enabled early identification of well appearing infants at high risk of sepsis. As a result, infected infants got prompt treatment averting progression to serious illness and death.

Adverse Events

No potential adverse events related to the study were identified.

5.9 Data Management and Statistical Analysis

To ensure good quality, data collection was uniform, quality assured laboratories were used for blood sampling. An updated research software (SPSS version 17.0) was used for data analysis and reporting.

Data recorded in the data collection tools was kept confidential and stored safely (under lock and key) by the principal investigator. A link log was used to code all personal details of the mother-baby pairs. Data was then retrieved from all questionnaires and newborn assessment forms and stored in a database. Data was then entered into computer using data entry screens incorporating range and consistency checks. Further cleaning was carried out after entry using frequency distributions and cross-tabulations until no more errors could be detected. Any errors which the investigator was unable to resolve was declared missing.

The software used was statistical products and service solutions (SPSS) version 17.0. Univariate analysis was done for the categorical variables (sex of baby, sepsis group etc) and descriptive statistics (means, medians, standard deviations) for continuous or discrete variables (such as birth weight). These results have been tabulated. Bivariate analysis was used to investigate any association between the response variable (Neonatal sepsis) with socio demographic and other variables of interest. The chi-square (χ^2) test was used to test association between 2 variables if categorical and satisfied all the conditions. If some chi-square assumptions were not met, Fisher's exact test was used instead.

6. RESULTS

This study was aimed to obtain the rate of sepsis in term newborns with risk factors of sepsis in the postnatal wards and of those with sepsis, determine the aetiology. A total of four hundred and forty nine mothers and their term newborns met the inclusion criteria over the study period and were recruited. One hundred and thirty nine (31%) of these newborns were found to be at risk of early onset sepsis whereas three hundred and ten (69%) of the newborns had no risk factors and were allowed home. The population of at risk newborns formed the subjects of the rest of the study (see flow chart below).

6.1 Baseline characteristics

The baseline characteristics of the mothers and newborns are shown in tables 1 and 2 below.

The mothers had a mean age of 27 years, a majority were married and had secondary level education. A majority of the mothers across all groups had attended ≤ 4 antenatal clinic visits. HIV sero-positive rates varied across the three groups with the proven sepsis group having the highest rate (25%) followed by probable and no sepsis groups at rates of 12% and 5 % respectively. The highest PROM rates were found in the proven sepsis group at 18% as compared to 10% and 5% in the probable and no sepsis groups respectively. The commonest mode of delivery was caesarian section across all the groups with rates of 83%, 88% and 73% in the proven, probable and no sepsis groups respectively (Table 1).

Only a few of the newborns had postdatism, 31%, 11% and 10% in the proven, probable and no sepsis groups respectively. Overall, the at risk newborns had good Apgar scores with a comparable mean above 8 across all three groups. A number of the newborns had low birth

weight, a majority of whom were in the probable sepsis group (27%) as compared to 12% in both the proven and probable sepsis groups. Females predominated in the proven and probable sepsis groups (56% and 58% respectively) whereas males predominated in the no sepsis group (56%)(Table 2).

Table 1 Baseline characteristics of mothers with newborns at risk of sepsis (n=139)

Characteristic	No sepsis n (%)= 41	Probable sepsis n (%)= 78	Proven sepsis n (%)= 16	P– value
Mother's age [Mean (SD)]	27.5(4.85)	27.53(5.66)	26.69(4.25)	0.839
Marital status				
Single	4(10)	14(18)	3(19)	0.457
Ever married	37(90)	60(77)	13(81)	
Educational level				
Primary	4(10)	14(18)	2(12.5)	0.596
Secondary	17(42)	37(48)	6(37.5)	
Post secondary	19(47)	26(34)	8(50)	
Antenatal clinic visits				
≤4 times	24(59)	55(70)	9(56)	0.26
>4 times	16(39)	21(30)	7(44)	
HIV Status				
Positive	2(5)	9(12)	4(25)	0.094
Negative	39(95)	68(88)	12(75)	
Duration of labour (hours)				
<18	38(93)	69(89)	10(62)	0.275
≥18	2(5)	8(10)	3(18)	
Mode of delivery				
SVD	11(27)	13(17)	2(12)	0.314
C/S	30(73)	65(83)	14(88)	

Table 2 Baseline characteristics of newborns at risk of sepsis (n=139)

Characteristic	No sepsis n (%)= 41	Probable sepsis n (%)= 78	Proven sepsis n (%)= 16	P– value
Gestation by dates				
37-40	37(90)	69(89)	11(69)	0.077
>40	4(10)	9(11)	5(31)	
Apgar score [Mean (SD)]	9.22 (0.75)	9(0.73)	8.82(1.38)	0.466
Birth weight (grams)				
<2500	5(12)	21(27)	2(12)	0.099
≥2500	36(88)	55(71)	14(88)	
Gender				
Male	23(56)	30(39)	7(44)	0.248
Female	18(44)	45(58)	9(56)	

A comparison was done between the different risk factors assessed; 87% of recruited newborns presented with maternal risk factors and only about 26% exhibited clinical features suggestive of sepsis. Both maternal and clinical risk factors were found in 17% of the newborns (Table 3).

Table 3 Distribution of risk factors for sepsis (n=139)

Risk factor	N	%
Maternal		
At Risk*	121	87.1
Not at risk	18	12.9
Clinical		
At Risk**	36	25.9
Not at risk	103	74.1
Maternal and Clinical		
At Risk***	23	16.5
Not at risk	116	83.5

*refers to newborns presenting with maternal risk factors

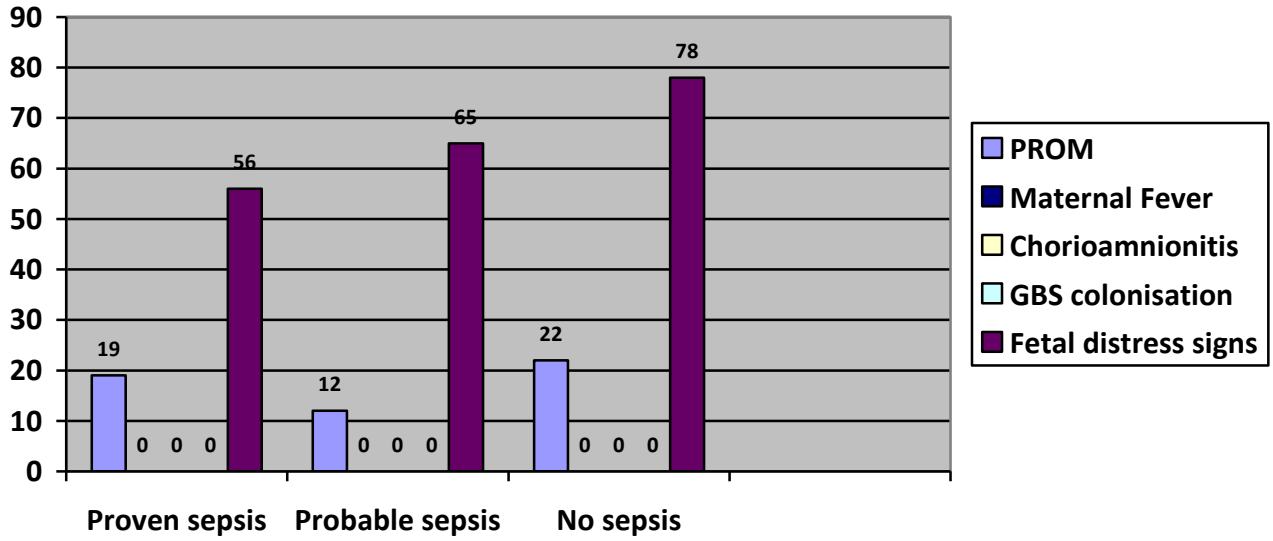
** refers to newborns presenting with clinical features of sepsis as a risk factor

***refers to newborns presenting with both maternal risk factors and clinical features of sepsis

6.2 Comparison of risk factors to sepsis

Maternal risk factors were then compared to sepsis outcome. PROM was the most common risk factor identified in those with proven sepsis, but was not unique to this group (p=0.275) (Figure 1).

Figure 1 Comparing maternal risk factors across the three outcome groups



Fetal distress, common across all the three groups, was not a unique identifier of sepsis in those at risk (p=0.709) (Table 4). Refusal to feed and grunting at an equal rate of 6% were the only clinical features identified in those with proven sepsis (Table 5). Several clinical features were identified in those with probable sepsis with a majority exhibiting refusal to feed (13%) and an absent suck reflex (13%).

Table 4 Comparing the most common risk factors to sepsis

Risk factor	No sepsis	Probable sepsis	Proven sepsis	P-value
Fetal Distress				
No	9(22.5)	20(26.7)	5(33.3)	0.709
Yes	31(77.5)	55(73.3)	10(66.7)	
PROM				
No	28(77.8)	61(85.9)	10(83.3)	0.568
Yes	8(22.2)	10(14.1)	2(16.7)	

Despite being classified into the "no sepsis" group, some of the newborns presented with clinical features of sepsis; 10% had refusal to feed, 2.5% lethargic, and 2% had tachypnoea. This had no clinical significance (Table 5).

Table 5 Comparing newborn clinical features with the three sepsis groups

Clinical feature	No sepsis n (%) = 41	Probable sepsis n (%) = 78	Proven sepsis n (%) = 16	P-Value
Breast feeding				
Normal	37(90).	65(83)*	15(94)	0.667
Difficult/refusal	4(10)	10(13)	1(6)	
Stimulation				
Appropriate	40(97.5)	68(87)	16(100)	0.184
Inappropriate/lethargic	1(2.5)	7(13)	0	
Moro's reflex				
No	0	3(4)*	0	0.311
Yes	41(100)	72(94)	16(100)	
Suck reflex				
No	4(10)*	10(13)*	1(6)	0.858
Yes	36(88)	64(83)	15(94)	
Palmar grasp reflex				
No	0	1(1.3)*	0	0.678
Yes	41(31.5)	73(94)	16(100)	
Anterior fontanelle				
Flat	39(95)	67(86)*	16(100)	0.474
Bulging	2(5)	8(10)	0	
Jaundice				
No	39(95)*	71(91)*	16(100)	0.152
Yes	0	5(9)	0	
Respiratory rate				
<60	40(98)	75(100)*	16(100)	0.327
>=60	1(2)	0	0	
Grunting				
No	41(100)	74(95)*	15(94)	0.341
Yes	0	2(2.6)	1(6)	
Chest wall indrawing				
No	41(100)	75(96)*	16(100)	0.685
Yes	0	1(1.3)	0	

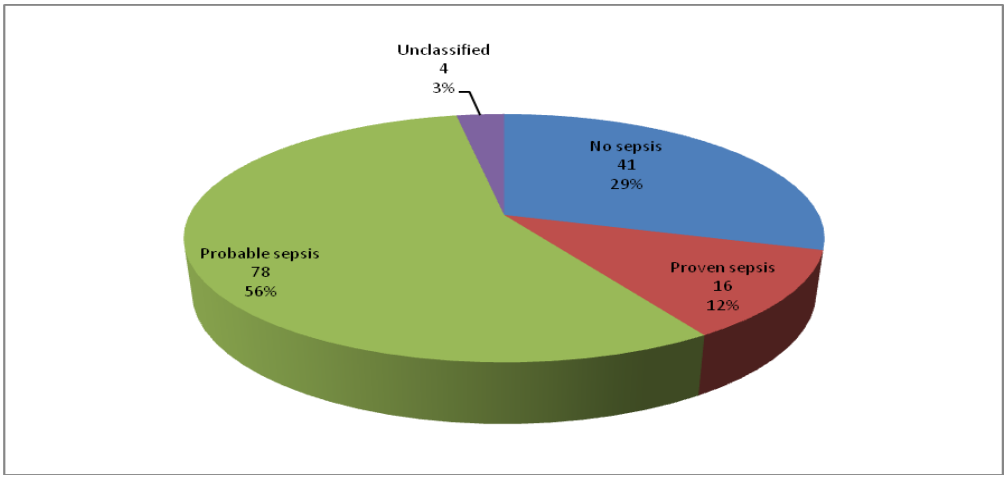
Column % = 100

* not adding up to 100 due to missing data

6.3 Distribution of Sepsis

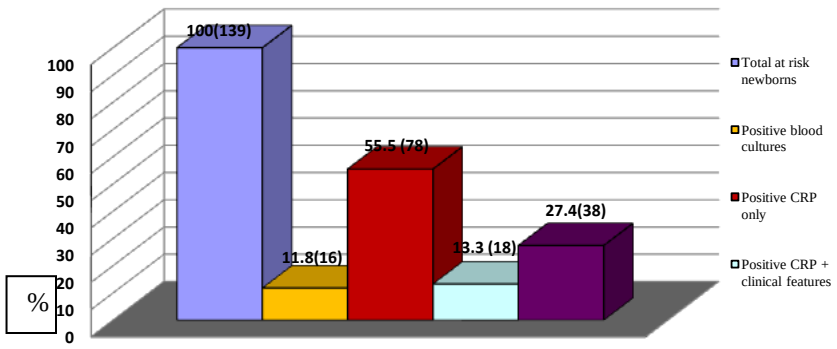
Out of the 139 newborns at risk, 16 had sepsis giving an early onset sepsis prevalence of 12%, 78 of them (56%) had probable sepsis and 41 (30%) had no sepsis**.** Approximately 3% were unclassified due to missing/misplaced results from the immunology and microbiology labs (Figure 2).

Figure 2 Sepsis classification of the newborns at risk (n=135)



As earlier noted, only one mother was reported to have received intrapartum antibiotic prophylaxis.

Figure 3 Mode of diagnosis in the newborns at risk (n=139)

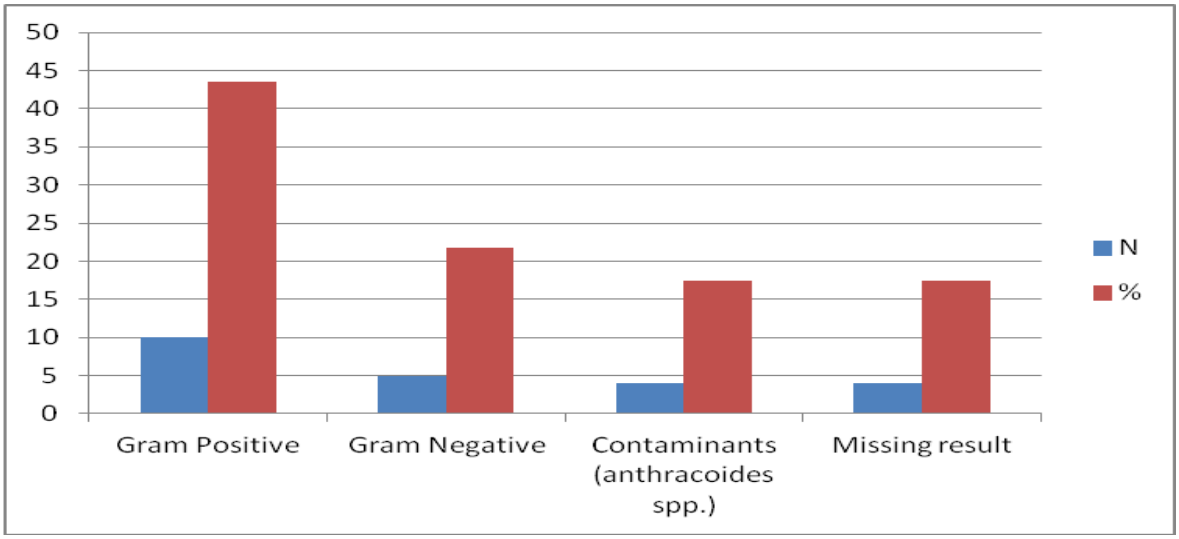


Based on the different modes of diagnosis, lab investigations informed a majority of diagnoses. Of those found to have probable sepsis, 55.5% were identified through CRP levels. Only 13.3% had clinical features suggestive of sepsis and a positive CRP (Figure 3). All except one of the positive blood culture babies had positive CRP levels.

6.4 Aetiology of Sepsis

The aetiological pathogens were mostly gram positive bacteria (the only gram positive isolate was coagulase negative Staphylococci). The gram negative bacteria isolated were Escherichia coli, Enterobacter spp. and Proteus spp. (Figure 4).

Figure 4 Aetiological pathogens



Crystalline penicillin and Gentamycin were used for empiric treatment of probable sepsis. Treatment was stopped after 48 hours in those with negative blood cultures and clinically stable. Similar antibiotics were used to treat the proven sepsis group for 10 days with favorable outcome.

6.5 Outcome

The newborns were followed up to the third day of life. Overall, 68% were alive and 2% died (all of whom had probable sepsis). Due to challenges with conducting the telephone follow up (wrong telephone numbers, unreachable numbers), 10.8% were lost to follow up (Table 8).

Table 8 Outcome of the newborns deemed at risk of sepsis

Outcome	No sepsis n(%)= 41	Probable sepsis n(%)=78	Proven sepsis n(%)=16
Died	0	3(100)	0
Alive	29(24.7)	73(62.4)	15(12.8)
Lost to follow up	12(86)	1(7)	1(7)

7. DISCUSSION

This study set out to look at the the proportion of term newborns in the post natal wards at risk of sepsis. This group was further evaluated for sepsis and causative agents identified.

The study revealed that of the term newborns admitted to the post natal wards, 31% were at risk of sepsis and of whom 12% had proven sepsis. These findings reveal the need to screen all newborns for sepsis during routine clinical practice. A study done in 2009-2010 at the Muhimbili National Hospital in Dar es salaam assessing the prevalence of sepsis,among other things, in 330 babies, both term (77%) and preterm (23%), mean age of three days, reported a proven sepsis rate of 22.4% (22). This higher rate could be explained by the addition of some preterms in the study population who pose a greater risk of having sepsis.

Refusal to feed and grunting were the most common clinical features associated with proven sepsis.Kumar similarly found feed intolerance as the most common clinical finding in those found to have sepsis, in addition to lethargy and irritability (20). However, this is in contrast to the Muhimbili study whose participants with fever and hypothermia were noted to have higher frequency of sepsis (22). This difference could be due to the variation in the population or missed opportunities in the wards of identifying fever/hypothermia (at night, primi parous women who may not be clear on what fever is). Patient education about newborn health should therefore be re-emphasized in our day to day patient management. Of note is that this study was limited to a three day follow up of the newborns via telephone interviews. A longer follow period of the babies and face to face interviews with the mother may have revealed more clinical features associated with proven sepsis. In addition, newborns in the proven and probable sepsis groups

were started on antibiotics empirically and this may have altered identified clinical features of sepsis.

PROM was the most common maternal risk factor in those with proven sepsis. However, this was not unique to the proven sepsis group as it was present in the probable and no sepsis groups. This is in contrast to a multi-center study done by Puopolo et al that estimated the probability of neonatal early onset infection based on maternal risk factors. Post-term delivery, maternal fever,and prolonged ROM were strong individual predictors of infection (17). Notably, the greatest percentage of post-term delivery was in the proven sepsis group . Advanced maternal age has been associated with early neonatal sepsis (22). A study done by Jiang et al postulates that once a woman's child bearing age is postponed, with an the extended period between the sexually mature phase and childbirth and an increase in the proportion of unplanned pregnancies, many women have induced abortions. This can lead to adverse effects on pregnant women and their newborns during delivery and following childbirth hence an increase in risk factors for neonatal sepsis (23). On the contrary, the mean maternal age of study participants was 27 years which may also explain the lower sepsis rates in this study as compared to other studies.

With just under a fifth of the probable sepsis group having concomitant clinical features, it may suggest that many newborns are being cleared as stable to go home yet are at risk of sepsis. This study revealed the commonest isolated pathogens were coagulase negative Staphyloccus aureus, followed by gram negative bacteria. Our findings differ from other studies which show Escherichia coli and GBS as the commonest cause of early onset neonatal sepsis worldwide (5-7). Kumar et al found CONS responsible for 4.5% of the proven infections in the newborn unit of KNH though the majority was by Enterobacter agglomerans (20).

The 2009-2010 Muhimbili study revealed Staphylococcus aureus as the commonest isolate, though, predominantly from pus swabs (21). Similarly, a ten year review study (2000-2009) done at Aga Khan University Hospital in one hundred and thirty two neonates revealed gram-positive organisms were the predominant cause of both early and late onset sepsis; their common isolates were staphylococcus epidermidis (34%) and staphylococcus aureus (27%).There were no isolates of group B streptococcus (24).

Almost 50% of the newborns were doing well by day 3. Unfortunately some were lost to follow up after discharge. Notably, all the 2% who died were from the probable sepsis group.

From the rising trend of sepsis rates from previous studies and findings from this study, keener clinical practice by clinicians is necessary for early diagnosis of sepsis.

8. CONCLUSION

There is a significant number of well appearing term newborns with sepsis in the post natal wards and as such require routine screening prior to discharge.

9. RECOMMENDATIONS

- Regular screening for sepsis of all newborns admitted to the post natal wards by paediatricians including assessment of maternal risk factors.
- A follow up study is necessary to further evaluate the group with probable sepsis who formed the majority in the postnatal wards.

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CONSENT FORM

Research Topic: Prevalence of early onset sepsis in "at-risk" term newborns in the postnatal wards of Kenyatta National Hospital

Investigator: Dr. Evelyne Ng'ang'a

Department of Paediatrics, University of Nairobi

Contacts: 0722 996341

Supervisors: Prof. Ruth Nduati, Department of Paediatrics, University of Nairobi

Prof. Fred Were, Department of Paediatrics, University of Nairobi

Dr. Rashmi Kumar, Department of Paediatrics, University of Nairobi

Introduction: Neonatal sepsis remains one of the leading causes of death in babies 0-28 days old. Early diagnosis and prompt treatment give these children a better chance of survival. Diagnosis remains a challenge due to non-specific clinical features and unavailability of rapid, accurate laboratory tests. This study looks to assess the magnitude of the problem in newborns at risk at Kenyatta National Hospital. It also looks to determine what causes the sepsis. This will help in early detection of sick newborns and prompt correct treatment.

Benefits: The results obtained will help clinicians identify the babies with sepsis and start immediate treatment. Selection of antibiotics will be based on the results. Results obtained will help in future identification of babies with sepsis early.

Risks: In order to determine presence of infection, a blood sample will be required to be obtained from the baby. This may cause some discomfort to the baby. All precautions will be taken against any unnecessary bleeding during sample collection.

Investigators note: This consent form is to give you a clear picture of the study, its benefits and associated risk. This is to guide you make an informed decision to have your baby participate in the study. Participation is completely voluntary. If you decide to participate, you may withdraw at

any time without consequences or explanation. The results of the study will be treated with strict confidentiality.

Parents/Guardians note: I have read the above information, or it has been read to me. I have had the opportunity to ask questions and all questions that I have asked have been answered to my satisfaction. In case I need more information I can contact Dr. Evelyne Ng'ang'a on 0722996341. I consent voluntarily to participate as a subject in this study and understand that I have the right to withdraw from the study at any time without affecting my further medical care in any way.

I, Mr./Mrs./Ms ----------, the parent

Of (child's name) ----------.

agree to the above and give consent for me and my child to be included in this study

As explained to me by----------

I understand the purpose of the study and conditions of participation.

Sign---------- Date----------

Witness Sign---------- Date----------

(Witness mandatory if the mother/caregiver cannot read)

I certify that _____received all information regarding the study, that she apparently understood it and she freely gave her consent to participate

Witness signature: _____

Date: _____

IDHINI

Swali la Utafiti: Ushamiri wa watoto walio katika hatari ya kuwa wagonjwa baada ya kuzaliwa katika wodi ya waliojifungua kwenye Hospitali ya Taifa ya Kenyatta.

Mpelelezi: Dr Evelyne Ng'ang'a

Idara ya Madaktari wa Watoto, Chuo Kikuu cha Nairobi

Mawasiliano: 0722 996341

Wasimamizi: Profesa Ruth Nduati, Idara ya Madaktari wa Watoto, Chuo Kikuu cha Nairobi.

Prof. Fred Were, Idara ya Madaktari wa Watoto, Chuo Kikuu cha Nairobi.

Dr Rashmi Kumar, Idara ya Madaktari wa Watoto, Chuo Kikuu cha Nairobi.

Utangulizi:Magonjwa ya damu (neonatal sepsis) yanaendelea kukumba watoto walio na umri wasiku 0 hadi 28. Vifo kutokana na magonjwa haya yanaendelea kuongezeka mno. Magonjwa haya yanahitaji utambuaji wa haraka. Matibabu ya haraka huwapa watoto hawa nafasi nzuri ya kuishi. Utambuaji bado ni changamoto kubwa kutokana na kutokuwa na alama za ugonjwa na ukosefu wa vipimo na kuwepo kwa maabara duni . Utafiti huu unaangazia ukubwa wa tatizo kwa watoto walio katika hatari kwenye Hospitali kuu ya taifa ya Kenyatta. Utafiti huu utasaidia utambuzi wa watoto walio katika hatari mapema na utaezesha uanzishaji wa matibabu haraka.

Faida: matokeo ya utafiti itasaidia hospitali kutambua watoto wagonjwa haraka, uanzishaji wa matibabu haraka na uteuzi wa dawa vilvyo.

Hatari/madhara: Kuezesha kutambua ugonjwa kwa mto, sampuli za damu zitahitaji kuchukuliwa kutoka kwa mtoto. Hii inaweza kusababisha uchungu na usumbufu kwa mtoto. Tahadhari zote zitachukuliwa dhidi ya kutoa kipimo cha damu zaidi ya kipimo kitakikanacho wakati wa ukusanyaji wa damu.

Mkaguzi: Idhini hii inaeleza wazi jinsi utafiti utafanywa, faida na hatari zinazohusika. Hii ni kukuwezesha kufanya uamuzi sahihi kabla ya kushiriki katika utafiti huu. Ushiriki ni hiari kabisa.

Unauwezo wa kuamua kutoshiriki kwenye utafiti huu wakati wowote bila madhara au maelezo. Matokeo ya utafiti yatashughulikiwa kwa siri.

Wazazi / Walezi: Nimesoma habari hii au nimeelezewa na kuelewa. Nimepewa nafasi ya kuuliza maswali na yote yamejibiwa kwa uridihi wangu. Nikihitaji maelezo zaidi naweza wasiliana na Dr Evelyne Ng'ang'a kupitia nambari ya simu 0722996341. Nimekubali kwa hiari kushiriki kama somo katika utafiti huu na kuelewa kwamba nina haki ya kutoka kwenye utafiti huu wakati wowote bila kuathirika kwa vyovyote vile wala kuhitakija kupeana sababu.

Mimi, Bwana /Bi ---------- ------, mzazi

wa (jina la mtoto) ---------- -------.

Nimekubali nilioelezewa na kutoa waamuzi kwa ajili yangu na mtoto wangu kushiriki katika utafiti huu

Kama ilivyoelezwa ni ---------- ----------

Naelewa lengo la somo na masharti ya ushiriki.

Ishara ---------- Tarehe ------- ----------

Shahidi Sign ---------- Tarehe ---------- ----------

(Ushahidi ni wa lazima kama mzazi/mlezi wa mtoto hawezi kusoma)

Ninathibitisha kwamba _____ameelezewa kwa upana na urefu kuhusu utafiti huu na ameelewa na kutoa amri ya kushiriki kwenye utafiti huu.

Shahidi: ……

Sahihi: ……..

Tarehe: ……

APPENDICES

APPENDIX 1

SCREENING QUESTIONNAIRE TO BE FILLED BY PRIMARY CARE GIVER

Date: ……

Study ID: …….

Age: ……

Marital status:

□ Single □ Separated

□ Married □ Divorced

Residence: …….

Educational level (tick as appropriate)

□ Primary school

□ Secondary school

□ College

□ University

Telephone no. ……

SECTION 1 – ANTENATAL HISTORY

1. Did you attend antenatal clinic? (Tick as appropriate)

□ Yes- MCH card seen

□ Yes- no MCH card seen

□ No

If yes, how many clinic visits ……

SCREENING FOR POSSIBLE MATERNAL INFECTION

2. Antenatal profile done (to obtain details from MCH card)

Parameter/Result	Positive	Negative	indeterminate
HIV			
VDRL			

Haemoglobin level (g/dl)……

Urinalysis report (tick as appropriate)

Clinic visit	Protein	Sugar	Bacteriuria	MCH card seen	MCH card not seen
1					
2					
3					
4					

3. Any history of dysuria (pain on passing urine) during pregnancy?

□ Yes

□ No

4. Any reported and documented fever 3 days before delivery? (circle your answer)

□ Yes

□ No

If yes, what was the temperature recording? ……^{o}c (see file)

5. Any history of abdominal tenderness 3 days prior to deliver?

    - ☐ Yes
    - ☐ No

6. Any antibiotic given within 4 hours of delivery?

    - ☐ Yes
        - ☐ < 4 hours to delivery
        - ☐ >4 hours to delivery
    - ☐ No

    If yes, which one(s)? (See file)…….

    - ☐ GBS specified antibiotic : penicillin, ampicillin, clindamycin, erythromycin, cefazolin, vancomycin
    - ☐ Broad –spectrum antibiotics: other cephalosporins, fluoroquinolones, extended spectrum lactams, or GBS specified antibiotic + aminoglycoside

7. Any history of foul smelling vaginal discharge/amniotic fluid? **(assesses perinatal risk factor of EOS)**

    - ☐ Yes
    - ☐ No

SECTION 2 – PERINATAL HISTORY

Screening for PROM and fetal distress

8. Labour

   Any drainage of liquour before labour?

   □ Yes □ No

   If yes:

   i. Duration of rupture of membranes? (hours) …….

   ii. Any meconium staining? (**assesses fetal distress**)

   □Yes □No

Duration of labour (hours) ……

Number of vaginal examinations ……(**assesses perinatal risk factor of EOS**)

9. Gestational age on delivery (tick as appropriate after calculation)

   LMP ……

   Date of delivery……

   □ 37 – 40 completed weeks

   □ > 40 weeks

10. Place of delivery

   □ KNH

   □ Other (please specify) ……

11. Mode of Delivery (tick as appropriate)

   □ Spontaneous vertex delivery

   □ Assisted delivery If yes, tick which one: □ Vacuum □ Forceps

- Not assisted
- Episiotomy

- Caesarian section (specify below)
  - C-section with labor, with ROM before C/S
  - C-section with labor, without ROM before C/S
  - C-section without labor, with ROM before C/S
  - C-section without labor, without ROM before C/S
  - C-section, not specified

12. Apgar score at 5 minutes……..

SECTION 3 – POSTNATAL HISTORY

13. Cord hygiene

Number of times cord is cleaned per day

- None
- at least once
- more than once

SUMMARY

MATERNAL RISK FACTOR	TICK (√) AS APPROPRIATE
Maternal fever ≥38ºC (100.4ºF)	
Chorioamnionitis	
5-minute Apgar score ≤ 6	
Fetal distress present	
Maternal GBS colonisation	
PROM ≥ 18 hours	
RISK (circle as appropriate)	YES NO

APPENDIX 2

NEWBORN ASSESSMENT FORM (to be filled in by researcher/ research assistant)

Date……..

1. Study ID: ……
2. Sex: male □ female □
3. Time since delivery: …….hours
4. Birth weight (kg)

SECTION 1 – ASSESSMENT OF RISK FACTORS OF SEPSIS (TICK AS APPROPRIATE)

- □ Birth weight < 2500g
- □ Prolonged rupture of membranes >18 hours
- □ Foul smelling liquor
- □ Multiple per vaginum examinations (> 4)
- □ Maternal fever (> 38.5 ^{0}c)
- □ Difficult or prolonged labour (>10hours primi, >8 hours multiparous)
- □ Aspiration of meconium/meconium stained liquour (MSL)

SECTION 2 - CLINICAL ASSESSMENT FOR SYMPTOMS AND SIGNS OF NEONATAL SEPSIS

PARAMETER (tick as appropriate)	0- 24 hours (day 1)	25-48 hours (day 2)	49-72 hours (day 3)
Breastfeeding Normal Difficult/refusal			
Response to stimulation Appropriate Inappropriate/lethargic			
Neonatal reflexes □ Moro's □ Suckling □ Grasp			
Anterior fontanelle □ Flat □ Bulging □ Sunken			
Palor (yes/no)			
Jaundice (yes/ no)			
Cyanosis (yes/no)			
Temperature (^{o}c)			
Pulse rate (beats/min)			
Respiratory rate(breaths/min)			
Grunting (yes/ no)			
Chest indrawing (yes/no)			
Umbilicus (clean/septic)			
History of convulsions (yes/no)			
RISK: (circle as appropriate)	**YES** **NO**	**YES** **NO**	**YES** **NO**

Section 3 - Laboratory Assessment for Sepsis

Direct assessment

1. Blood culture

   Organism grown

   - Yes (specify) ……
   - No

Indirect assessment

2. CRP titre ……(no units)

   - Multiply titre by conversion factor 6 to get exact level (mg/l) ……..

Section 4 - Possible Environmental Risk Factors

1. Number of mothers in the room: _____
2. Any coughing mothers in the room? Yes No

   If yes, duration of cough : < 2 weeks > 2 weeks
3. Estimated number of visitors per newborn (daily)……..
4. No. of people who handle the newborn (other than mother) per day……
5. Assess hand washing practices in those that those that handle the newborns:

   - Mother before breastfeeding
   - Mother after washroom visit
   - Mother after changing diapers
   - Visitors before picking/handling the baby