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PREVALENCE OF SEPSIS AMONG NEONATES ADMITTED TO KISII LEVEL 5 HOSPITAL

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ABSTRACT

Introduction; **Infections are the third commonest cause of death in the neonate, with the vast majority of deaths occurring in resource limited countries such as Kenya which has a neonatal mortality rate of 22 per 1000 live births according to the Kenya Demographic and Health Survey, 2014.**

Objectives: **To determine the prevalence, pattern of bacterial causes and the economic and socio-demographic factors associated with sepsis in neonates admitted to Kisii Level 5 Hospital.**

Design: **A descriptive cross- sectional study.**

Setting: **Newborn Unit and Paediatric Wards of the Kisii Level 5 Hospital.**

Subjects: Eighty neonates admitted at Kisii Level 5 Newborn Unit and Paediatric wards.

Methods: **Out of a study population of 406, consecutive sampling was done until the sample size of 80 neonates with clinical definition of sepsis was achieved. Sepsis was defined as refusal to breastfeed, convulsions, lethargy, fast breathing, grunting, nasal flaring, severe lower chest wall in- drawing, fever ≥ 37.5oC or hypothermia <35.5oC, deep jaundice involving palms and soles of the feet, ten or more pustules, umbilical redness extending to the periumbilical skin, pus draining from the ear and central cyanosis. These neonates had blood taken for full blood count and culture with sensitivity.**

Results: **The prevalence of clinical sepsis was 19.7% (95% CI 15.9- 23.9). Neonatal sepsis was significantly associated with maternal dysuria (p= 0.018). There were no significant associations between socio -demographic factors and neonatal sepsis.**

Conclusion: **Neonatal sepsis contributes to a significant proportion of neonatal admissions to Kisii Level 5 Hospital.**

INTRODUCTION

Neonatal sepsis is an invasive bacterial infection occurring during the first four weeks of life. Infections are the third most common cause of deaths in the neonate, contributing 10- 20% of the deaths in this age group, the majority of which are in resource limited countries such as Kenya whose current neonatal mortality rate is 22 deaths per 1000 live births.[1] As neonatal deaths contribute to 56% of deaths in infants in Kenya, the 3rd Sustainable Development Goal's target, as well as the *Every Newborn Action Plan goal of less than 10 deaths per 1000 live births by the year 2035* will not be achieved without addressing mortality in the neonate. [1]

A study by Berkley et al from August 1998 to July 2002 at Kilifi District Hospital in Kenya involving young infants, defined as less than 60 days old showed the prevalence of community acquired culture proven sepsis as 12.8% [2]. Ng'ang'a et al in 2013 found that the prevalence of proven sepsis in term newborns in the postnatal wards of Kenyatta National Hospital (KNH) was 12% [3]. The organisms that cause early onset neonatal sepsis within the first 72 hours of life include GBS, *H. influenza, L. monocytogenes and C. trachomatis*. [4]. Organisms that cause late onset neonatal sepsis after 72 hours of life include Coagulase- Negative Stapylococcus (CONS), *Klebsiella spp, Enterobacter, E. coli, Serratia marcescens, Pseudomonas spp and Staphylococcus aureus (S. aureus)* [4]. Opiyo et al found that gram negative bacteria were a commoner cause of sepsis than gram positive bacteria [5].

Neonatal sepsis is the systemic inflammatory response syndrome in the presence of or as a result of suspected or proven infection [6]. Neonatal infection occurs due to compromise of the barriers to infection offered by the placenta and membranes, pathogenicity of the colonizing organism and incompetence of the neonatal defense mechanisms. Neonates exhibit physiologic immunodeficiency that is more marked in premature, stressed and sick infants and which accounts for their susceptibility to infection. [7]. In term neonates the levels and function of complement is two- thirds that in the adult and in preterms it is less than 50%. [7].

The signs of neonatal sepsis described by Opiyo et al facilitated case finding of young infants with severe disease and best predicted the need for hospital based care [8]. They included a history of feeding difficulty, history of convulsions, axillary temperature equal to or greater than 37.5^{o}C or less than 35.5^{o}C, change in activity level, respiratory rate above 60/minute, severe chest in-drawing, grunting and cyanosis [8].

The current recommended empiric treatment of suspected neonatal sepsis by the WHO is ampicillin or penicillin and gentamicin for patients less than 2 months of age. Second line treatment consists of flucloxacillin for *S. aureus* infections and third generation cephalosporins. Cloxacillin is given in place of penicillin for extensive skin pustules or abscesses [9]. Community based studies such as Berkley et al in 2005 showed antimicrobial susceptibility of 88% for penicillin with gentamicin and 97% for ampicillin with gentamicin[5]. Local prevalence susceptibility results are stated as the most important factor for local empiric antibiotic regimes while data from provinces and districts are essential for representative or balanced global data [10].

While blood cultures are the gold standard for detection of bacteremia in newborn infants with suspected sepsis, many infants who are septic may have negative blood cultures [11]. In 1988, Rodwell et al used full haemogram parameters as a screening tool for neonatal sepsis [12]. The system assigns a score of 1 for each of 7 parameters including: abnormal total leukocyte count, abnormal total neutrophil count, elevated immature

polymorphonuclear (PMN) count, elevated immature to total PMN ratio, immature to mature PMN ratio equal to or more than 0.3, platelet counts equal to or less than 150, 000/mm^3 and pronounced degenerative changes in PMN [12]. The total score is then interpreted using a standard scoring system to determine the likelihood of neonatal sepsis. With a score equal to or less than 2, the likelihood that sepsis is absent is 99%. The higher the score, the greater the likelihood of sepsis [12]. The study concluded that the scoring system improved the diagnostic accuracy of the full haemogram as a screening tool for neonatal sepsis [12].

Mukhopadhya et al found that neonates born at 34 to 36 weeks had a 2-3 times higher incidence of early onset sepsis as compared to those born at 37 to 40 weeks. [13]. There was a steep increase in the risk of GBS in early onset sepsis when rupture of membranes exceeded 18 hours as this provided the opportunity for ascending colonization of placental and fetal tissues. [13].

MATERIALS AND METHODS

Study design: A descriptive cross- sectional study was carried out.

Study site: The Newborn Unit and Paediatric Wards of the Kisii Level 5 Hospital. The Newborn Unit has an average of 140 admissions every month and the paediatric ward which admits infants older than 21 days receives an average of 10 infants per month.

Study period: Three-month period between March and May 2014

Study population: The study population comprised neonates less than 28 days old admitted to the Kisii Level 5 Newborn Unit and Paediatric wards whether they were born in the hospital or elsewhere.

Sample size determination: Was determined using the Fischer test. The sample size was 80. The prevalence was taken from the study by Berkley et al at Kilifi District Hospital in Kenya, in which the prevalence of community acquired culture proven sepsis in neonates and young infants ranged from 10% to 16% [2]. Thirteen percent was selected as the median figure and used to calculate the sample size.

Screening criteria: All infants aged less than 28 days seen at the hospital were identified. Neonates who met the inclusion criteria were examined for clinical signs of sepsis. The neonates were consecutively enrolled into the study until the sample size required was recruited.

Inclusion criteria: Infants aged less than 28 days, born at gestational age of 34 weeks and above who had a birth weight equal to or greater than 1500g and whose mothers gave consent.

Study procedure: Neonates admitted were screened and consecutive recruitment was done until the desired sample size was achieved. Demographic, social and economic data was collected from consenting mothers. No inducements were offered. Information given was strictly used for research purposes and entered into a predesigned data collection form.

Definition of clinical sepsis: An infant with any of the danger signs of serious bacterial infection according to the Pocket Book of Hospital Care for Children from the World Health Organization [9]; history of inability to breastfeed, history of convulsions, lethargy or unconsciousness, respiratory rate more than 60 breaths per minute on two separate counts, grunting, nasal flaring, severe lower chest wall in- drawing, fever ≥ 37.5^{o}C or hypothermia <35.5^{o}C, jaundice involving palms and soles of the feet, ten or more pustules or a big abscess, umbilical redness extending to the periumbilical skin, pus draining from the ears and central cyanosis.

Infants with clinical evidence of sepsis had blood taken for a full blood count with peripheral blood film and culture and

sensitivity testing at the Aga Khan Kisumu laboratory annex in Kisii town. The laboratory has RIQUAS (Randox International Quality Assessment Scheme) and HUQAS (Human Quality Assessment Services) for quality control.

Blood culture processing: The blood culture method used was manual. Two milliliters of blood obtained by venepuncture before administration of antibiotics were inoculated into a culture bottle containing brain heart infusion broth which was then transported to the laboratory within one hour for incubation. The bottle was incubated at 37^0 and monitored for visible signs of bacterial growth including turbidity above the red cell layer, hemolysis, gas bubbles and clots. If these signs were seen, a subculture was done onto blood agar (for anaerobic incubation for 48 hours), chocolate agar (incubation in carbon dioxide atmosphere for 48 hours) and MacConkey agar incubated aerobically overnight). Positive growth would have proceeded for microorganism identification. If no growth was seen, incubation was prolonged to 5 days.

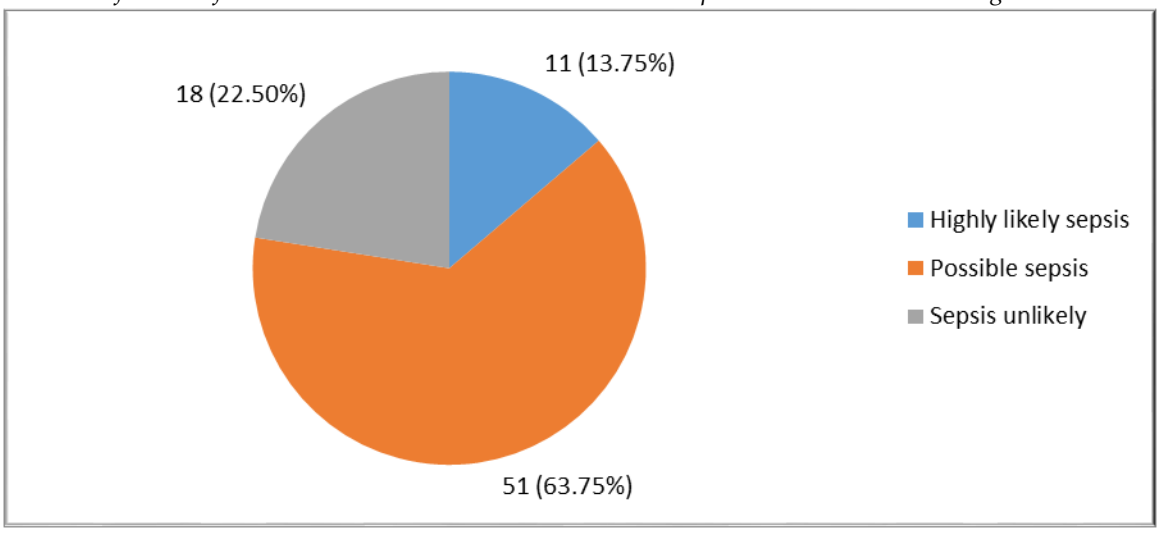
RESULTS

Prevalence of clinical neonatal sepsis: During the period from March to May 2014, a total of 406 neonates were admitted to Kisii Level 5 Hospital. They were all screened for the clinical signs of sepsis and the inclusion criteria. Of the 406 neonates in the study population, a subset of 80 neonates had clinical sepsis and the prevalence of neonatal sepsis was therefore 19.7% (95% CI 15.9- 23.9). All the 80 blood cultures carried out on recruited neonates were negative. The hematological score described by Rodwell was used to draw futher diagnostic inference from the full haemogram samples taken.

Classification of neonatal sepsis using the hematological scoring system (HSS): Figure 1 below represents the classification of sepsis among the 80 patients with clinical signs of sepsis based on the HSS. A HSS of less than 2 means that sepsis is unlikely, a score of 3- 4 means that sepsis is possible and a score equal to or greater than 5 means that sepsis is highly likely. Eleven (13.8%, 95% CI 7.1- 23.3) neonates had scores indicating a highly likely sepsis diagnosis, 51 (63.8%, 95% CI 52.2 to 74.2) had scores compatible with a diagnosis of possible sepsis and 18 (22.5%, 95% CI 13.9- 33.2) were unlikely to have sepsis.

Figure 1

Classification of the babies admitted with clinical neonatal sepsis based on the Hematological Score



Clinical features of babies admitted with clinical neonatal sepsis: Table 1 below summarizes the frequency of the clinical features of sepsis among the admitted neonates. The most common clinical features were fever (n = 51, 63.8%), refusal to feed (n = 39, 48.8%), and chest in- drawing (n = 24, 30%). Fast breathing (respiratory rate > 60 breaths per minute on two separate counts) was documented in 22 (27.9%) of neonates and skin pustules occurred in 18 (22.5%) neonates. Clinical features rarely seen included: deep jaundice, umbilical redness extending to periumbilical skin, pus draining from ears and marked abdominal distention with each of these features occurring in only a single neonate for each sign.

Table 1

Clinical features of neonates admitted with clinical neonatal sepsis

CLINICAL FEATURE	FREQUENCY	PERCENT (%)
Fever/ hypothermia	51	63.8
Refusal to breastfeed	39	48.8
Chest in- drawing	24	30.0
Abnormal respiratory rate above60/min, below 20/ min or apnea more than15 seconds.	22	27.9
Skin pustule/ abscess	18	22.5
Nasal flaring	10	12.5
History of convulsions	8	10.0
Grunting	8	10.0
Drowsy/ lethargic	7	8.8
Others*	4	5.0

* Includes one case each for; deep jaundice involving palms and soles of the feet, Umbilical redness extending to the periumbilical skin or the umbilicus draining pus, pus draining from ear(s) and marked abdominal distention

Association between neonatal sepsis and maternal characteristics: Table 2 shows the association between maternal factors and neonatal sepsis. Among maternal characteristics, the factor that was significantly associated with neonatal sepsis

was dysuria, which was reported in 45 of the mothers. Neonates who were classified as highly likely to have sepsis according to the HSS were 8.2 times more likely to have a mother who reported a history of dysuria than a neonate who was classified as unlikely to have sepsis. (p= 0.018).

Table 2

Association between neonatal sepsis and materenal characteristics

CHARACTERISTIC	UNLIKELY-SEPSIS (N = 18)	POSSIBLE SEPSIS (N = 51)	HIGHLY LIKELY – SEPSIS (N =11)	UNLIKELY VS POSSIBLE P VALUE	OR (CI)	UNLIKELY VS HIGHLY LIKELY P VALUE	OR (CI)
Maternal age							
16-19 years	2(11.1)	3(5.9)	1(9.1)	NA	1.0	NA	1.0
20-24 years	10(55.6)	30(58.8)	7(63.6)	0.598*	0.2 (0.1-19.9)	1.000*	1.4 (0.1-94.2)
25-29 years	6(33.3)	18(35.3)	3(27.3)	0.597*	2.0 (0.1-21.8)	1.000*	1.0 (0.04-78.4)
30-35 years	0(0.0)	5(9.8)	2(18.2)	0.444*	NA	0.400*	NA
Dysuria	1(5.6)	7(13.7)	5(45.5)	0.670*	2.7 (0.3-128.9)	0.018*	8.2 (0.7-407.9)
Recent febrile illness	1(5.6)	2(3.9)	1(9.1)	1.000*	0.7 (0.03-43.3)	1.000*	1.7 (0.02-141.2)
Maternal marital status							
Married	16(88.9)	47(92.2)	11(100.0)	0.647*	1.5 (0.1-11.3)	0.512*	NA
Highest level of education							
Primary	2(11.1)	1(2.0)	0(0.0)	NA	1.0	NA	NA
Secondary	9(50.0)	34(66.7)	11(100.0)	0.138*	7.6 (0.3-458)	0.476*	NA
Tertiary	7(38.9)	16(31.4)	0(0.0)	0.268*	4.6 (0.2-286)	NA	NA
Maternal occupation							
Formal employment	4(22.2)	6(12.0)	0(0.0)	NA	1.0	NA	NA
Self employed	4(22.2)	7(14.0)	2(18.2)	1.000*	1.2 (0.1-9.5)	0.467*	1.0
Subsistence farmer	4(22.2)	12(24.0)	0(0.0)	0.664*	2.0 (0.3-14.9)	NA	NA
Housewife	6(33.3)	25(50.0)	9(81.8)	0.222*	2.8 (0.4-16.5)	0.087*	3 (0.3-41.1)
Water source							
Treated tap water	6(33.3)	23(45.1)	9(81.8)	NA	1.0	NA	1.0
Well	7(38.9)	19(37.3)	1(9.1)	0.087	0.7 (0.3-3)	0.074*	0.1 (0.001-1.2)
River	5(27.8)	9(17.6)	1(9.1)	0.290	0.5 (0.1-2.5)	0.149*	0.1 (0.003-1.8)

* Fischer exact test

DISCUSSION

The study revealed that the prevalence of clinical neonatal sepsis at Kisii Level 5 Hospital was 19.7%. After application of the hematological scoring system, it was found that 13.8% of neonates were highly likely to have sepsis. In the study by Berkley et al done from 1998 to the year 2002 at Kilifi in Kenya the prevalence of community acquired culture proven sepsis was 12.8% [2]. The commonest clinical features of neonatal sepsis were fever or hypothermia, refusal to breastfeed, chest wall in- drawing and fast breathing (respiratory rate above 60 breaths/ minute). According to Opiyo et al, refusal to breastfeed and fast breathing were among some of the clinical features most valuable in estimation of risk of severe illness in neonates [5].

In the study by Onyedibe et al, neonates born at home had the highest percentage of culture proven sepsis [14]. Even though there was no significant association in this study between place of delivery and sepsis, this lack of association may have been due to the small sample size. It was found that 95% of mothers delivered in a hospital. Other studies found that a significant number of neonates born in health facilities developed sepsis [6, 15]. This was because most mothers labored for prolonged periods at home and presented to hospital late and because the hospital environment is likely to have a larger concentration of infective microorganisms. In this study 96.3% of the mothers had durations of membrane rupture that were less than 18 hours by the time they arrived in hospital, indicating a need to improve standards of care and infection prevention control during and after delivery.

The blood cultures undertaken in this study were all negative. The positivity of blood cultures in the study by Berkley et al was 12.8% [2]. Blood cultures are not free from error and can be falsely sterile as has been demonstrated in some postmortem cultures [11]. The possible reasons for the low yield of blood cultures include insufficient sample volumes and intermittent or low density bacteremia [11]. One milliliter of blood should be the minimum when pediatric culture bottles are used for detection of low level bacteremia of 4 CFU/ml and less. Blood cultures obtained in adequate volumes are twice as likely to give a positive result. The standard blood volume inoculated into the culture media in the study was at least 2ml. The lower limit recommended for paediatric bottles is 1ml [16]. The culture bottles available for the study were standard bottles, not particularly paediatric. There are a number of factors that could have contributed to the negative findings in the study. The bactericidal activity of blood that is innate immunity (complement, phagocytic white blood cells, and lysozyme) can reduce the viability of organisms [16]. Liquid cultures dilute bactericidal activity. The volumes for media used in paediatric bottles should be 20- 40 ml. The blood should be 10- 20% of the total medium volume [16]. As the culture bottles used were not paediatric culture bottles, the blood to broth ratio was not strictly adhered to. Different blood culture technologies are available. Manual systems involve incubation of liquid culture media with frequent inspection and microscopy with blind plating onto solid medium culture to see if any growth had occurred. Modern closed computer based systems assess changes in carbon dioxide every 10- 15 minutes as an indicator of bacterial growth [16]. It has been found that 25% of infants with sepsis have low colony count bacteremia and two- thirds of those younger than two months of age have counts less than 10 CFU/ml [17]. This could have contributed to nil bacterial recovery at culture of the blood from these young infants.

Even though blood cultures are more sensitive (82%) and specific (96%) indicators of presence of potentially fatal bacterial infection, negative cultures can occur in the presence of significant bacterial illness [18]. In a study by Seale et al, 17 % of neonates with fatal illness associated with bacterial infection had negative pre- mortem blood cultures [18].

Even though blood cultures give a definitive diagnosis, they are time consuming with a turnaround time of 48- 72 hours, are low yielding (from 8- 73%) and the test's reliability depends on the laboratory it was conducted in [19]. A study carried out by Makkar et al evaluated the performance of the Hematological Scoring System (HSS) of Rodwell et al 1988 for the purpose of early detection of sepsis in high risk infants and to improve the diagnostic accuracy of full haemogram as a screen test [19]. It was found that 83.3% of patients with culture proven sepsis had haematological scores above five, which shows that the HSS has a good correlation with culture positive sepsis [19].

The HSS has the advantage of being applicable to neonates even when receiving antibiotic therapy and being the single test that is easily available in most hospitals [20]. There was a significant association between dysuria and sepsis (neonates highly likely to have sepsis were 8.2 times more likely to have a mother who reported a history of dysuria than a neonate who was classified as unlikely to have sepsis, p= 0.018). A follow up study should be done with a larger sample size, utilizing the more sensitive automated method of detecting bacterial growth so that microbial and sensitivity patterns can be appreciated.

CONCLUSION

The prevalence of sepsis among neonates admitted to Kisii Level 5 Hospital was 19.7% and neonates with sepsis were more likely to have been born to mothers with dysuria.

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