PREVALENCE OF ACUTE KIDNEY INJURY AND ITS RISK FACTORS FOR SEVERITY IN NEONATES WITH SUSPECTED SEPSIS AT KENYATTA NATIONAL HOSPITAL

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H58/75545/2014

A DISSERTATION IN PARTIAL FULFILLMENT FOR THE DEGREE OF MASTERS OF MEDICINE (PAEDIATRICS AND CHILD HEALTH), UNIVERSITY OF NAIROBI.

2016
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DECLARATION

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This dissertation is my original work and has not been presented for the award of a degree in any other university

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ACKNOWLEDGEMENTS

I wish to express my appreciation to:
The University of Nairobi Department of Paediatrics, my supervisors for their guidance and support, patience and valuable comments and criticism throughout the study.

The Department of Research and Programmes, KNH.

All the children and caregivers for their willingness to participate and patience during the study period.

My study assistants, Evans Nambafu, and Phillip Ayieko for working selflessly and helping me throughout the study period.

My friend and colleague Dr. Rose Jalang’o for her support and finally my husband Phillip and children Desmond and Danilla for their great support.
DEFINITION OF TERMS

**Acute Kidney Injury:** A sudden decline in renal function with decline in the glomerular filtration rate, resulting in a disturbance in nitrogenous waste excretion, loss of water and electrolyte regulation and acid base balance dysregulation.

**Suspected sepsis:** Diagnosis is made when at least two of the general symptoms fever or hypothermia, lethargy, poor feeding and one or more of the systemic symptoms: Respiratory symptoms include tachypnoea, grunting and intercostal retractions. Cardiovascular system symptoms consist of reduced capillary refill peripheral hypoperfusion, cyanosis, tachycardia or bradycardia. Central Nervous System systems consist of irritability, bulging fontanelles and altered muscular tone.

**Oliguria:** urine output to the level of less than 0.5ml/kg/hr for more than 6hours.

**RIFLE acronym:** Risk Injury Failure Loss and End stage renal disease, it is a criterion for evaluating AKI based on rising serum creatinine levels and urine output measurement.

**High serum creatinine levels:** for the purposes of this study in neonates cut off levels of 100µmmols/l was used.

**Term newborn:** defined as baby born ≥37 weeks of gestation up to one month of age. Gestation age will be calculated from the last menstrual period by Naegele’s rule.
ABBREVIATIONS

AKI:  Acute Kidney Injury
AKIN:  Acute Kidney Injury Network
ATP:  Adenosine Triphosphate
DIC:  Disseminated Intravascular Coagulopathy
DAMPS:  Damage Associated Molecular Patterns
GFR:  Glomerular Filtration Rate
ICAMS:  Intracellular Adhesion Molecules
KDHS:  Kenya Demographic Health Survey
KIDGO:  Kidney Disease Improving Global Outcomes
KNH:  Kenyatta National Hospital
NSAIDS:  Non-Steroidal Anti Inflammatory Drugs
PAMPS:  Pathogen Associated Molecular Patterns
RAAS:  Renin Angiotensin Activating System
RIFLE:  Risk Injury Failure Loss End Stage
SCR:  Serum Creatinine
TNF:  Tumor Necrosis Factor
VCAMS:  Vascular Cell Adhesion Molecules
WHO:  World Health Organisation
ABSTRACT

Background

Acute Kidney Injury (AKI) is characterized by a sudden decline in renal function resulting in the inability of the kidneys to excrete nitrogenous wastes. The criteria for neonatal AKI vary among different studies. Serum creatinine levels of 1.5mg/dl have been used as cut off levels for AKI case definition (1). The causes of neonatal AKI can be prerenal, renal and post-renal; however prerenal azotemia is the most common type of AKI found in the neonates (85%) (2).

The WHO global observatory has neonatal sepsis amongst the leading causes of neonatal mortality accounting for 400,000 neonatal deaths globally per annum (3). Sepsis is often complicated by multiple organ dysfunctions and due to the unique aspects of neonatal renal physiology; acute kidney injury (AKI) often complicates sepsis.

Objectives

The primary objective was to determine the prevalence of acute kidney injury in neonates with suspected sepsis admitted at Kenyatta National Hospital. Our secondary objective was to determine the neonatal and maternal factors that are associated with AKI severity in the study population. Sepsis is a common cause of morbidity in neonates, establishing its association with AKI was intended to drive a high index of suspicion and facilitate prompt diagnosis and treatment to improve neonatal outcomes.

Methods

We carried out a hospital based cross-sectional study in which neonates admitted with suspected sepsis were evaluated for AKI by measuring their serum creatinine levels. Neonates with a serum creatinine of 100μmmols/l or more were considered to have AKI. We monitored the neonates urine output for 24hrs, and also administered questionnaires to the mothers who had consented to the study and whose neonates had met the inclusion criteria. Data on the risk factors were obtained and subsequently we classified AKI severity by the neonatal RIFLE criteria. Data was analyzed using (SPSS) version 21. Chi square tests were conducted to analyze the relationship between the dependent and the independent variables. ANOVA was used for linear data.
Results

There were 352 newborns admitted to the KNH paediatric wards during the study period, of these, 332 newborns met the clinical criteria for the diagnosis of suspected sepsis and of these 120 cases of acute kidney injury were found, yielding a prevalence of 36.1% (95% CI 31 to 41.6). The most common AKI presentation based on the neonatal RIFLE criteria was Failure at 72 (62.6%, 95% CI 53.6 to 71.6), followed by Injury 26 (22.6%;95% CI 14.8 to 30.4). There were 17 (14.8%; 95% CI 8.2 to 21.3) newborns classified as Risk.

The 24 hour urine output per kilogram body weight was 1.8 ± 1.1. Serum creatinine levels ranged from 188 to 1027µmol/l with a mean of 393.3±200.5. Based on the neonatal characteristics versus the AKI risk, there was a significant association between AKI and age of neonate (ANOVA p=0.04). Neonates classified as having AKI risk were on average aged 8.3 days compared to those with injury (mean=12.8 days±7.1) and those in failure (mean =12.2days ± 5.2 days). The post hoc analysis showed that the difference in age between the neonates at risk and those with injury was statistically significant (Bonferroni P =0.035) while that between injury and failure or risk and failure was not significant. The mean gestational age (p = 0.823) and birth weight (p =0.767) were not associated with AKI.

The maternal demographics that had significant association with AKI were maternal fever in the week preceding delivery and the presence of a post-partum complication of either puerperal sepsis or post-partum hemorrhage at p=0.041 and p=0.038 respectively. All the other maternal socio-demographic and labor related factors had no significant association with AKI.

Conclusion

The prevalence of AKI among neonates with suspected sepsis was 36.1%. Neonates with late onset sepsis were more likely to develop AKI than those with early onset sepsis. The presence of maternal fever in the week preceding delivery and post-partum complications were associated with severe form of AKI in the neonates.
INTRODUCTION AND LITERATURE REVIEW

Acute Kidney Injury in the neonatal population has shown a rising trend in the recent past. The unique aspect of neonatal renal physiology predisposes newborns to develop AKI rapidly. The exact prevalence of AKI remains unknown and this is further complicated by the diverse case definitions used in the available studies. Globally, efforts are being made to develop a standardized evidence based case definition of neonatal AKI and evaluate its associated risk factors, under the neonatal kidney collaborative that recently conducted a multicentre Assessment Of Worldwide Acute Kidney Injury Study (AWAKEN) (4).

The WHO defines neonatal sepsis as a clinical syndrome of bacteria colonization with systemic signs and symptoms of infection in the first 4 weeks of life (5). Sepsis is a leading cause of neonatal mortality accounting for 400,000 deaths globally per annum (3). Kenya Demographic Health Survey 2014 revealed that neonatal mortality rate is 22 deaths per 1000 live births (6). Findings from a previous study conducted at Kenyatta National Hospital revealed that neonatal sepsis was the leading cause of death followed by prematurity and perinatal asphyxia that are often complicated by sepsis (7).

Sepsis has consistently been linked to the occurrence of acute kidney injury in neonatal populations contributing to about 78% of the cases (8). A study done in India by Majumdar et al, established that 52 out of 200 neonates with sepsis developed AKI with prematurity and low birth weight being additional risks for sepsis related AKI (9). Sepsis is characterized by a generalized inflammatory response that activates the coagulation and fibrinolytic cascades resulting in endothelial injury. This results in systemic hypotension, hypo perfusion and renal ischemia with altered function (10).

AKI is a clinical diagnosis that requires a high index of suspicion to recognize reduced urine output and subsequently the confirmation of the diagnosis by laboratory evaluation of serum urea, creatinine and electrolytes. AKI independently increases morbidity and mortality in neonates with sepsis, mortality has been documented to be as high as 70.2 % in sepsis associated AKI (9).
Neonatal Renal Physiology
There are unique aspects of neonatal renal physiology that increase vulnerability to develop AKI. Nephrogenesis begins in the 5th week of gestation and is completed at about 34-35 weeks and therefore preterm newborns and those who suffered IUGR have increased susceptibility to develop AKI (11). Upon the cessation of the fetal circulation, renal blood flow increases progressively from 6% of the total blood volume at birth to 20% by the 6th week of life. During this transitional period, any insult that causes hypoperfusion predisposes to rapid development of AKI (12).

The Renin Angiotensin System (RAS) is also critical in the normal renal development and renal blood flow. The RAS vasoconstricts both the afferent and efferent arterioles while the prostaglandins mediate vasodilatation. Dysregulation of these counter regulatory hormones often occurs in critically ill neonates leading to a rapid decline in glomerular function. This is further worsened by medications e.g. NSAIDS and nephrotoxic antibiotics like the aminoglycosides frequently used to manage sepsis (11).

The GFR (Glomerular Filtration Rate) at birth is about 10 to 20ml/min/1.73m² and it steadily rises to the adult GFR by the 2nd year of life. Any conditions resulting in renal ischemia further lower the GFR in this critical neonatal period. Tubular function is also immature with decreased concentrating ability and thus poor handling of water and electrolytes (12). These additional aspects have implications of increasing susceptibility to develop AKI and they affect drug choices and dosage in the management of these neonates.

The normal serum creatinine levels in a term newborn ranges from 68.1 to 76.6µmmols/l. Two readings taken 24 hrs. apart are required although a clearly elevated single reading beyond the normal range is sufficient for diagnosis of renal dysfunction. The serum creatinine level in AKI would subsequently rise by 42- 88µmmols/l/day (2).

Risk Factors and Etiology
The risk factors for the development of AKI include; very low birth weight (VLBWt) <1500gms, perinatal asphyxia, respiratory distress syndrome, need for mechanical ventilation at birth, maternal drug administration like the non-steroidal anti-inflammatory drugs and antibiotics. Alaro et al in a study at KNH established that the prevalence of AKI in perinatal asphyxia was 11.7 %. The mortality in those neonates with AKI was at 71.4% (13).
another study by Koralkar et al found the prevalence of AKI in VLBWt neonates at Cincinnati children Hospital in Birmingham of 18% with a mortality of 42% (14).

The causes of AKI can be prerenal, renal and post renal. In the neonatal period, 85% of AKI cases are prerenal with prompt resolution of renal function and urine output once the systemic hypoperfusion is reversed (15).

**Pathophysiology of Acute Kidney Injury in Sepsis**

There is a paucity of data on the precise pathophysiology of acute kidney injury in neonatal sepsis. Previously, sepsis induced AKI was thought to occur as a result of impaired renal macrocirculation resulting from global renal ischemia. A study conducted in Italy by Zarbok et al re-evaluating the pathophysiology of kidney injury during sepsis concluded that AKI can occur in the presence of normal or increased renal blood flow, implying that significant renal impairment can occur prior to the development of septic shock and its resultant hemodynamic instability. The inflammatory responses that occur during sepsis induce adaptive changes to the tubular epithelial cells to minimize energy demands and enhance survival. These changes result in reduced kidney function (16).

Sepsis is characterized by a cascade of adaptive and maladaptive cellular mechanisms which potentiate each other to give rise to AKI. These include endothelial dysfunction, inflammation and coagulation disturbances. Pathogen-associated molecular pattern molecules (PAMPs) are usually derived from microorganisms and get recognized by pattern recognition receptor (PRR)-bearing cells of the innate immune system as well as many epithelial cells. Damage-associated molecular pattern molecules (DAMPs) are derived from the host cell and they initiate and sustain immunity in response to trauma, ischemia, and tissue damage, either in the absence or presence of pathogenic infection. PAMPs and DAMPs bind specific receptors [Toll-like receptors, NOD-like receptors, RIG-I-like receptors, AIM2-like receptors, and receptors for advanced glycation end products (RAGE)] to promote autophagy, a cell survival mechanism invoked in response to environmental and cellular stress (17). The kidney which receives about 20% of the cardiac output is amongst the earliest organs to get in contact with these pro inflammatory mediators. PAMPs and DAMPs can exert their effects either via the peritubular microcirculation or as they are filtered through the glomerulus to cause local inflammatory mediated cellular damage (18).
Microvascular Dysfunction

Sepsis causes significant alteration in microvascular blood flow in the entire body; the kidneys are not spared. The hallmark of microvascular dysfunction is in the increase in heterogeneity in the distribution of blood flowing in the capillaries. This results in hypoperfusion and hypoxia that worsens the damage caused by inflammation. The areas of microvascular dysfunction have sluggish peritubular flow and thus delayed transit time for RBCs and leukocytes creating a hypercoagability state. These processes further mediate inflammation via elaboration of VCAMs and ICAM-1 amplifying the proinflammatory signals (17).

Oxidative stress triggers tubular injury with resultant epithelial tubular vacuolization and functionally down regulation of metabolism through prioritization of energy consumption. Other cell preservation mechanisms include cell cycle arrest and mitophagy (mitochondrial removal) often triggered by oxidative stress and inflammation (19). Mitochondrial dysfunction particularly in the proximal tubule that results in a reduction in ATP (Adenosine Triphosphate) production impairs ATP dependent pump functions and thus the derangements in the urea and electrolytes that occur in AKI (20), (9). These self-preservation mechanisms preserve the cells regenerative capacity upon resolution of the injurious stimulus and they also intercept the pro-apoptotic process and prevent cell death (21), implying that timely intervention on the pathophysiologic process allows recovery and resumption of normal renal function.

During sepsis, increased vascular permeability occurs with resultant interstitial edema and fluid retention. Tissue edema increases the diffusion distance for oxygen to the tissues and because the kidney is an encapsulated organ, edema worsens microcirculation perfusion as it alters the transmural pressures and aggravates venous congestion (22).

Diagnosis of Acute Kidney Injury in Neonates

There is no internationally acceptable case definition of AKI in neonates. The KIDGO guidelines define AKI as an increase in serum creatinine of more than 0.3mg/dl (>26.5µmol/l) within 48 hours, an increase in serum creatinine 1.5 times the baseline, and urine output of 0.5ml/kg/hr for 6 hours (23). AKI has no distinct clinical presentation and therefore its diagnosis requires that its predisposing factors are identified during history and examination. Oliguria or anuria may be the only positive findings in the presenting history.
that can point to AKI (2). A high index of suspicion is required to make a diagnosis of AKI and this suspicion should be confirmed with evaluation of renal function in all sick neonates.

**Neonatal RIFLE**

RIFLE is an acronym for Risk Injury Failure Loss and End stage. It is a standard classification criteria for AKI that employs both serum creatinine and urine output. It describes the continuum of the syndrome of AKI in increasing severity with Risk at the early phase and end stage as the terminal phase. It targets to address the milder forms of AKI with a potential of worsening that should be promptly managed to avert the adverse outcomes (24).

In the pursuit of standardization of AKI diagnosis in neonates, Ricci and Rocco recently made adjustments on the paediatric RIFLE factoring in the unique aspects of neonatal renal physiology discussed above by increasing urine output cut off from 0.5 to 1.5mls/kg/hr. The p-RIFLE was found to be too restrictive in the neonatal population who had higher total body water and immature tubular development and function (24).

In a study to validate the use of the RIFLE criteria in neonates, Mohkan et al in Iran compared the RIFLE criteria and the old ARF (Acute Renal Failure) definition. They determined the RIFLE score for each neonate and urine output on the second day of admission. AKI was found in 77.5% of the neonates, 43% in the Risk category, 51% at Injury, and 6% at Failure in comparison with the old definition of ARF which had a rate of 3.2%. This study concluded that the RIFLE criteria can detect neonatal AKI in neonates and it’s a good predictor for mortality in critically ill neonates (25). We intend to use the neonatal RIFLE criteria for our study by measuring the serum creatinine at admission and urine output monitoring within the first 24 hours of admission.

**Suspected Neonatal Sepsis: Clinical Criteria**

Early diagnosis of sepsis in neonates is crucial for their survival. Clinical signs and symptoms of sepsis in neonates vary by gestational age and the severity of the disease process (26). The WHO Young Infant Study Group, conducted a multicentre study in developing countries on the key clinical signs in neonates that strongly predict the presence of a serious bacterial infection. They developed and validated a simplified clinical prediction model with three vital signs: temperature, respiratory rate and weight for age, and seven specific clinical findings: inability to suck, crepitations, cyanosis, history of convulsions, definite lower chest wall indrawing, failure to arouse with minimal stimulation and history of change in activity.
These clinical signs were then scored to estimate the probability of a serious bacterial infection in the infant. In its simplest form, the model was able to predict the probability of serious illness as having an ROC area of 0.866 (27). This study informed the WHO guidelines for the management of sick young infants and validated its utility.

Michael English et al in a study on Kenyan infants in Kilifi, aged <60days evaluated key signs and symptoms that were pointers to severe disease in neonates. Data from this study had a more specific set of signs that included: feeding difficulty, abnormal behavior, fast breathing, chest wall indrawing, cyanosis, and bulging fontanelles as useful predictors of very severe disease with 97% specificity and 56% sensitivity.

Kanyange et al conducted a study on the predictors of positive blood cultures and death in neonates with suspected neonatal sepsis in a tertiary hospital in Mwanza Tanzania. They used the WHO criteria for diagnosis of sepsis in neonates and found that, clinical findings that were predictors of a positive blood culture in neonates with early and late onset neonatal sepsis were: Inability to feed, lethargy, cyanosis, meconium stained liquor, premature rupture of membranes and convulsions. 300 neonates with a clinical diagnosis of suspected sepsis were evaluated. 47% of neonates with early onset sepsis had positive blood cultures, in comparison to 51.4% of those with late onset neonatal sepsis (28).

The 2013 WHO guidelines for hospital management of sick newborns (29) has the following key characteristic features of likely sepsis that guide inpatient management of sick newborns:

• Inability to feed.
• Fast breathing with a respiratory rate of >60 breaths/minute
• Lower chest wall indrawing.
• Nasal flaring, grunting and central cyanosis.
• Temperature <35.5°C and >38°C
• Less than normal movement.
• Lethargy, altered consciousness, convulsions.
• Bulging fontanelles.
• Red umbilical stump with pus discharge.
• Skin pustules.

These clinical examination findings together with collaborating history of likely sepsis in the mother in the immediate peripartum period justify a clinical diagnosis of suspected sepsis and forms a basis for the prompt initiation of treatment as the septic screen is being carried out to confirm sepsis.
There is evidence that AKI does occur early in the presence of sepsis (16). Evaluating its prevalence at the time when a clinical diagnosis of suspected sepsis is being made, we will aid in making appropriate interventions in the management of these neonates. For instance, the first line antibiotic recommendations for suspected sepsis includes an aminoglycoside and penicillin; Aminoglycosides are known to be nephrotoxic. This study will provide a basis for further research in terms of appropriate choice of antibiotics in the management of neonatal sepsis. Renal health in the neonatal period pauses a critical challenge in terms of early recognition of kidney injury as well as renal protection in the management of frequently occurring neonatal conditions like neonatal sepsis (43). Timely initiation of an appropriate antibiotic to manage sepsis is key considering that AKI can occur quite early in the pathophysiology of sepsis. The WHO guidelines for the management of possible serious bacterial infection in the neonate recommends the use of a penicillin and Aminoglycoside as 1st line antibiotics (44). There are studies that have found ototoxicity as an adverse effect of aminoglycoside use but evidence for nephrotoxicity is still lacking due to the primary challenges of diagnosing AKI in neonates.

Misiime et al in a systematic review to assess the risk of gentamycin toxicity in neonates treated for possible serious bacterial infection in middle and low income countries, found a 3% risk of ototoxicity. Ten studies on nephrotoxicity were reviewed, 5 studies reported no nephrotoxic event, 3 studies had events in both the intervention and comparison group and 1 study had a single nephrotoxic event but the infant was on indomethacin as well. Due to the variations in AKI case definitions a meta-analysis on nephrotoxicity was not feasible (45). Early recognition of AKI is therefore very crucial in determining appropriate antibiotic choice to effectively treat sepsis but at the same time preserve the kidney from further damage.

Another important aspect to consider is the quality of care given at the initial episode of AKI due to the fact that it pauses a long term risk for chronic kidney disease and mortality. Greenberg et al conducted a systematic review on the long term risk of chronic kidney disease and mortality after an episode of AKI and found 3.1(95% CI 2.1-4.1) for proteinuria, 1.4 (0.9-2.11) for hypertension, 6.3 (5.1-7.5) for declining GFR, 0.8 (0.4-1.4) for end stage renal disease, 3.7 (2.8-4.5) for mortality (46). Timely diagnosis and timely initiation of dialysis are key to effectively managing neonatal AKI particularly in our set up where most of the neonates were received in AKI failure and required dialysis.
A Summary of Related Studies

There is scarce data on AKI prevalence in the neonatal population and its global prevalence remains unknown. The available studies evaluate AKI in special populations i.e. the low birth weight, the critically ill in NICU (Neonatal intensive care unit), and AKI in neonates with perinatal asphyxia (30).

Mathur et al conducted a study in India on the occurrence of AKI in neonatal sepsis. They found an AKI incidence of 26% amongst the neonates with sepsis. The AKI case definition used was a BUN of >20mmols/l. Of the 200 neonates admitted with sepsis, 52 developed AKI. The mortality for those who developed sepsis induced AKI was 70.2% versus 25% in those without AKI. This study also revealed that of the neonates with AKI, only 15% had oliguria, in keeping with other studies that concluded that most neonatal AKI is non oliguric (31), (8).

In another study evaluating acute kidney injury in neonatal sepsis at a university hospital in Orissa India, Pradan et al found that out of 120 neonates with sepsis, 33 had AKI. Majority of these had the non oliguric type. Mortality amongst those who had AKI was 54.5% in comparison with 24% mortality among those without AKI. The case definition of AKI in this study was a serum creatinine of 1.5mg/dl (133µmol/l). Shock and DIC were additional risk factors for mortality in the neonates with sepsis and AKI (32).

Ahasenali M Holda et al, in a study on the effect of neonatal septicemia on renal function, evaluated 449 neonates for AKI and its associated risk factors. 104 cases of AKI were found with case fatality of 51.9% amongst those neonates with sepsis who developed AKI in comparison with a fatality of 21% for those with sepsis in the absence of AKI. Oliguria was found in 13.5% of the cases. This study had AKI case definition based on a BUN of >45mg/dl on 2 separate occasions more than 24hrs apart (17).

Vachvanichsanong et al in a 10 year retrospective study at a tertiary hospital in Thailand, a developing country, sought to establish the prevalence of AKI, its etiology, mortality and risk factors for mortality in neonates. The findings revealed a rising incidence of AKI over the 10 year period with a 0.9%, 4.5% and 6.3% incidence over the first second and third quarters of the ten year study period respectively. Vachvanichsanong et al used a serum creatinine level of >2mg/dl (176µmol/l) with the cut off for urine output at 1ml/kg/hr. Sepsis was still found
to be the leading cause of AKI at 30.9% with a mortality of 61.5% in those who had sepsis induced AKI (33).

These four studies evaluated the association between sepsis and AKI confirming that sepsis induced AKI is indeed a common phenomenon associated with significant mortality, drawing valuable conclusions that inform neonatal care management. Our study borrowed significantly from these studies as they were conducted in resource limited settings.

**Table 1: A Summary of Related Studies**

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Study title</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mathur et al 2006</td>
<td>Occurrence of AKI in neonatal sepsis</td>
<td>AKI was present in 52 of the 200 neonates (26%) with a 70.2% (p&lt;0.001) mortality in those with asphyxia induced AKI. AKI was predominantly non oliguric.</td>
</tr>
<tr>
<td>2. Pradan et al 2009</td>
<td>A study of acute kidney injury and neonatal sepsis.</td>
<td>AKI was found in 27.5% of the cases and was predominantly non oliguric. Mortality amongst those with sepsis induced AKI was 54.5%.</td>
</tr>
<tr>
<td>3. Vachvanichsanong et al.</td>
<td>Prevalence of AKI in a tertiary hospital in Thailand, a developing country.</td>
<td>Sepsis was the commonest cause of a AKI at 30.9% with the highest mortality.</td>
</tr>
</tbody>
</table>
Study Justification
About 80% of neonates admitted to paediatric wards at Kenyatta National Hospital have suspected sepsis at the time of admission as a clinical diagnosis (7). The clinical prediction of the likelihood of occurrence of AKI in these neonates was intended to drive a high index of suspicion for prompt diagnosis and timely initiation of management to avert poor outcomes.

The AKI prevalence in the paediatric intensive care unit at KNH was found to be 85.5% (34) yet the prevalence in the neonatal population remained unknown.

Studies have shown that AKI is not only associated with short term high mortality and morbidity outcomes, but also a high risk of long term renal outcomes following an initial episode. This includes hypertension, proteinuria, progression to Chronic Kidney Disease (CKD) and a reduction in overall long term survival (33). This implies that the care given after an initial episode of AKI is important in averting long term renal dysfunction, thus knowledge on prevalence will increase vigilance to promptly diagnose and effectively manage cases.

An Additional local utility in the study hospital is for planning and procurement purposes to provide diagnostics and treatment supplies to manage neonatal AKI cases.

A key component to reduce neonatal mortality is to improve case management of specific conditions as a key component of comprehensive newborn care. Knowledge on prevalence and associated risk factors will empower clinicians with knowledge to tailor their interventions appropriately.

The selected study populations are the neonates seen outside the newborn unit and the results of this study can be generalized to other facilities attending to sick newborns.

STUDY OBJECTIVES

Primary Objective
To determine the prevalence of Acute Kidney Injury in neonates with suspected sepsis admitted to Kenyatta National Hospital.
Secondary Objective
To determine the maternal and neonatal risk factors associated with AKI severity in neonates with suspected sepsis.

METHODOLOGY

Study Design
This was a hospital based cross sectional study.

Study Area
The study was conducted at Kenyatta National Hospital (KNH) which is the largest national teaching and referral hospital in Kenya located in Nairobi County, a few kilometers from the central business district. It has a bed capacity of 1800. There are 4 pediatric wards each with a bed capacity of 100 and a specialized newborn unit. Its primary mandate is to offer specialized health care services. Of interest to this study are the newborn and renal services. It is the main inpatient hospital for the low and middle income population in Nairobi and its environs.

The paediatric wards at Kenyatta National Hospital admit approximately 120 to 180 neonates a month. These neonates are mostly transfers in from other hospitals. The neonates admitted to the wards are those who weigh >2000gms and >37weeks gestation at birth. The New Born Unit (NBU) carters for preterm and low birth weight newborns as well as sick term neonates delivered in KNH.

Study Population
The study population consisted of neonates admitted with a clinical diagnosis of suspected sepsis into the paediatric wards at Kenyatta National Hospital.

Recruitment of Study Participants
The investigator screened all neonates at admission using the observation checklist appendix 1 for clinical signs and symptoms of suspected sepsis. Vital signs and anthropometric data were recorded for each of the newborns. Blood samples were then collected for serum urea and electrolyte analysis and those whose creatinine levels exceeded 100µmol cut off level were recruited into the study.
Inclusion Criteria

- This study included all neonates admitted to Kenyatta National Hospital with suspected sepsis aged 0-28 days.
- Written consent provided by mother/guardian.

Exclusion Criteria

- Neonates who had a confirmed diagnosis of congenital renal malformations.
- Neonates who developed AKI after surgery.
- Neonates admitted before day 3 of life.

Sample Size Calculation

The sample size was determined using Cochran’s Formula for Sample Size Determination in Prevalence studies:

\[ n = \frac{z^2 p (1 - p)}{d^2} = \frac{1.96^2 \times 0.25 \times 0.75}{0.075^2} = 119 \]

- \( n \) = Sample Size
- \( z \) = Normal Standard Deviation taken with a 95% Confidence Interval; set at 1.96.
- \( p \) = Expected Prevalence of Acute Kidney Injury at 25% in a study by Pradan et al in India (35)
- \( d \) = Study Precision taken as 7.5%.

A study sample of 120 was taken.

Sampling Technique

Consecutive sampling technique was used. All newborns admitted with suspected sepsis who met the inclusion criteria were enrolled within the first 24 hours of admission both night and day.

Study Period

The study was conducted over a four month period between August 2016 and December 2016.

STUDY VARIABLES

Dependent Variable

Diagnosis of acute kidney injury based on serum creatinine levels of >100\(\mu\)mmol/l.
Independent Variables

Maternal Factors

Age, parity, marital status, level of education, occupation, place of delivery, duration of hospital stay after delivery, mode of delivery, maternal risk factors for sepsis, fever, prolonged rupture of membranes, urinary tract infection.

Neonatal Factors

Sex, gestational age, birth weight, feeding mode, feed intervals, age at diagnosis, documented urine output.

Study Outcomes

This study achieved the following outcomes:

- Determination of the prevalence of AKI in neonates admitted with suspected sepsis.
- Description of maternal and neonatal factors associated with AKI severity in neonates with suspected sepsis.

DATA COLLECTION PROCEDURE

Pretesting of the questionnaire was done at the study site before the start of actual data collection to assess reliability and validity of the questionnaire.

The entry point was neonates admitted with suspected sepsis who were evaluated at admission using the observation checklist by the principal investigator in the paediatric emergency unit (See Appendix I).

In all neonates, serum creatinine was routinely determined at the time of admission. We assessed serum creatinine levels after day 3 of life. AKI was defined as serum creatinine level above 100µmmols on after day three of life.

Informed written consent was then sought for the confirmed AKI cases by the principal investigator and the research assistants once the patient had been settled in the admitting ward.
The anthropometric data of the case was collected by the principal investigator and the research assistants. This was followed by administration of the questionnaire to the mothers who consented to the study.

The neonates urine output was then monitored for 24 hours from the time of diagnosis of AKI by either urine collection bags or a urinary catheter inserted aseptically. A 24 hour urine output was documented. (Appendix IV)

After the 24 hour period the neonatal RIFLE criteria was used to classify the neonates’ severity of AKI. (Appendix V)

The collected data was then entered and analyzed.
Figure 1: Study Flow Diagram

Entry point: Neonates with suspected sepsis

Obtain informed consent from those who meet the inclusion criteria Sr cre>100μmmol/l

24 hr urine output monitoring

RIFLE classification done

Data entry and analysis
Data Management and Analysis
The questionnaires were reviewed daily to check for completeness. The responses in the questionnaires were then tabulated, coded and processed.

Data was analyzed using Statistical Package for Social Sciences (SPSS) Version 21.

Chi square tests were conducted to analyze the relationship between the dependent (AKI) and the independent variables (neonatal age, sex, birth weight, maternal factors: Parity, presence of fever in the week preceding delivery, level of education and socio economic status).

Data on the risk factors was analyzed by 2 by 2 tables and chi square for categorical data and comparison of means by ANOVA for linear data.

Frequency tables and graphs were used to present the data.

Control of Bias and Errors
1. Measurement bias - The questionnaire was pretested to reduce insensitive measure bias, ensuring the questions are sensitive enough to detect the important difference in the variable of interest.
2. Sampling bias - Only those who met the eligibility criteria were included.
3. Information bias - Each research assistant was familiarized with the study and the questionnaire. They were trained on the study objectives and procedures. The principal investigator assessed the responses given in the questionnaire on daily basis to ensure validity of collected data.

Ethical Consideration
Approval to conduct the study was sought from the UON pediatrics department and the KNH/UoN, Ethical Review Committee. Approval from the Kenyatta National Hospital administration was also sought. Parents and caregivers were given a full explanation of the study and a written consent was obtained. Emergency care and resuscitation were carried out before research related procedures. No additional beneficial treatment was given to study subjects as an incentive to participate in the study. All the information received about the study subjects was treated with utmost confidentiality.
RESULTS

Prevalence of AKI in Suspected Neonatal Sepsis
Out of the 332 neonates admitted to KNH with suspected sepsis during the study period a total of 120 had AKI yielding a prevalence of 36.1% (95% CI 31 to 41.6). The classification of AKI diagnosis is presented in figure 2. The most common AKI presentation was failure 72 (62.6%; 95% CI 53.6 to 71.6), followed by injury 26 (22.6%; 95% CI 14.8 to 30.4). There were 17 (14.8%; 95% CI 8.2 to 21.3) children classified as risk.

Figure 2: AKI Classification based on Neonatal RIFLE in Neonates with Suspected Sepsis

Characteristics of the Neonates with AKI
The mean age of the neonates with suspected sepsis who were diagnosed with AKI was 11.2 days (SD ± 5.6). Approximately one-quarter (24.9%) of the neonates were in the early neonatal age group. There were 68 (56.7%) males, giving a male-to-female ratio of approximately 4:3. All the neonates were delivered at term (mean gestational age 39.1 weeks, SD ± 1.6), and had normal birth weight 111 (92.5%). The mean birth weight was 3216 gms (SD ± 513).
Table 2: Characteristics of Neonates with AKI

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Frequency n = 120</th>
<th>Percent %</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>68</td>
<td>56.7%</td>
<td></td>
</tr>
<tr>
<td>Mean age in days ± SD</td>
<td></td>
<td></td>
<td>11.2(± 5.6)</td>
</tr>
<tr>
<td>Early neonatal period (&gt;7days)</td>
<td>29</td>
<td>24.6%</td>
<td></td>
</tr>
<tr>
<td>Late neonatal period (&gt;7days)</td>
<td>89</td>
<td>75.4%</td>
<td></td>
</tr>
<tr>
<td>Mean birth weight ± SD</td>
<td></td>
<td></td>
<td>3216(±513)</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>9</td>
<td>7.5%</td>
<td></td>
</tr>
<tr>
<td>Normal birth weight</td>
<td>111</td>
<td>92.5%</td>
<td></td>
</tr>
<tr>
<td>Mean gestation in weeks ± SD</td>
<td></td>
<td></td>
<td>39.1(± 1.6)</td>
</tr>
<tr>
<td>Term births</td>
<td>120</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

Renal Functions of Neonates with AKI

Urine output and serum creatinine levels in neonates with AKI and suspected sepsis are summarized in the box and whiskers plots. The 24-hourly urinary output ranged from 3mls to 286mls with a mean output of 123.2 ± 67.4. The mean output in milliliters per kilogram body weight was 1.8 ± 1.1. Serum creatinine levels ranged from 118 to 1027 µmol/l with a serum creatinine level of 393.3 ±200.5.
Figure 3: 24 Hour Urine Output Volume

Figure 4: Urine Output (per kg body weight)
Neonatal Characteristics and AKI Severity

There was a significant association between AKI and age of neonate (ANOVA p = 0.04), as shown in table 3. Neonates classified as having AKI risk were on average aged 8.3 days compared to those with injury (mean = 12.8 days ± 7.1) and those in failure (mean = 11.2 days ± 5.2). Post-hoc analysis showed that the difference in age between neonates at risk and those with injury was statistically significant (Bonferroni P = 0.035) while that between injury and failure or risk and failure was not significant. Mean gestational age (p = 0.823) and birth weight (p = 0.767) were not significantly associated with AKI.

Table 3: Association between AKI Severity and Neonatal Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Risk Mean ± SD</th>
<th>Injury Mean ± SD</th>
<th>Failure Mean ± SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in days</td>
<td>8.3 ± 4.6*</td>
<td>12.8 ± 7.1*</td>
<td>11.2 ± 5.2</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean gestation (weeks)</td>
<td>39.1 ± 1.2</td>
<td>39.2 ± 1.5</td>
<td>39 ± 1.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Mean birth weight (grams)</td>
<td>3229 ± 522</td>
<td>3263 ± 512</td>
<td>3181 ± 512</td>
<td>0.7</td>
</tr>
</tbody>
</table>
Table 4: Summary of Maternal Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Frequency n=120</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20 years</td>
<td>12</td>
<td>10%</td>
</tr>
<tr>
<td>21-29 years</td>
<td>73</td>
<td>60.8%</td>
</tr>
<tr>
<td>&gt;30 years</td>
<td>25</td>
<td>20.8%</td>
</tr>
<tr>
<td><strong>Occupation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salaried/self employed</td>
<td>53</td>
<td>48%</td>
</tr>
<tr>
<td>Unemployed/casual</td>
<td>62</td>
<td>57.1%</td>
</tr>
<tr>
<td><strong>Marital Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>85</td>
<td>70.8%</td>
</tr>
<tr>
<td>Single</td>
<td>35</td>
<td>29.1%</td>
</tr>
<tr>
<td><strong>Level of Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>primary education</td>
<td>28</td>
<td>23.3%</td>
</tr>
<tr>
<td>secondary education</td>
<td>58</td>
<td>48.3%</td>
</tr>
<tr>
<td>Tertiary education</td>
<td>29</td>
<td>26%</td>
</tr>
<tr>
<td><strong>Place of Delivery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KNH delivery</td>
<td>27</td>
<td>22.5%</td>
</tr>
<tr>
<td>Delivered in other facility</td>
<td>82</td>
<td>72.8%</td>
</tr>
<tr>
<td><strong>Mode of Delivery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>75</td>
<td>62.5%</td>
</tr>
<tr>
<td>Ceasarian section delivery</td>
<td>32</td>
<td>28.5%</td>
</tr>
<tr>
<td><strong>Primiparity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>68</td>
<td>56.6%</td>
</tr>
<tr>
<td><strong>Maternal fever</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>89.8%</td>
</tr>
<tr>
<td><strong>Meconium stained liquor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>71</td>
<td>63.8%</td>
</tr>
<tr>
<td><strong>Post partum hemorrhage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>4.1%</td>
</tr>
<tr>
<td><strong>Postpartum sepsis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>4.1%</td>
</tr>
<tr>
<td><strong>Duration of stay &lt; 48hrs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>68</td>
<td>60.8%</td>
</tr>
<tr>
<td><strong>History of UTI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.83%</td>
</tr>
</tbody>
</table>

**Maternal Characteristics**

The modal age of mothers was 20-29 years - 76 (60.8%) with a mean age of 26 years (± 5.9), as shown in Table 4. Most of the mothers 68 (56.6%) were primi gravid, and reported that they were married - 85 (70.8%). Most of the neonates we saw were referrals having been delivered at other facilities - 82 (72.8%). The mothers of the neonates with AKI had a short duration of hospital stay post-partum of less than < 48 hours – 68 (60.8%).
Table 5: Association of Maternal Characteristics and AKI Severity

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Risk n = 17 (%)</th>
<th>Injury n = 26 (%)</th>
<th>Failure n = 72 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 years</td>
<td>2 (11.7)</td>
<td>2 (7.6)</td>
<td>8 (61.5)</td>
<td>0.5</td>
</tr>
<tr>
<td>20-29 years</td>
<td>10 (58.8)</td>
<td>15 (57.6)</td>
<td>48 (63.2)</td>
<td></td>
</tr>
<tr>
<td>30 years +</td>
<td>5 (29.4)</td>
<td>9 (52.9)</td>
<td>12 (44.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Parity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primi parity</td>
<td>13 (76.7)</td>
<td>11 (42.3)</td>
<td>44 (61.1)</td>
<td>0.07</td>
</tr>
<tr>
<td>Multi parity</td>
<td>4 (23.5)</td>
<td>15 (57.6)</td>
<td>28 (38.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Marital Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>5 (29.4)</td>
<td>4 (15.3)</td>
<td>21 (29.1)</td>
<td>0.6</td>
</tr>
<tr>
<td>Married</td>
<td>12 (70.5)</td>
<td>22 (84.6)</td>
<td>51 (70.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Occupation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salaried/informal employment</td>
<td>9 (52.9)</td>
<td>14 (53.8)</td>
<td>30 (41.6)</td>
<td>0.6</td>
</tr>
<tr>
<td>Casual worker/unemployed</td>
<td>8 (47)</td>
<td>12 (46.1)</td>
<td>42 (58.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Level of Education</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>5 (29.4)</td>
<td>9 (34.6)</td>
<td>14 (19.4)</td>
<td>0.4</td>
</tr>
<tr>
<td>Secondary</td>
<td>9 (52.9)</td>
<td>9 (34.6)</td>
<td>40 (55.5)</td>
<td></td>
</tr>
<tr>
<td>Tertiary</td>
<td>3 (17.6)</td>
<td>8 (30.7)</td>
<td>18 (25)</td>
<td></td>
</tr>
<tr>
<td><strong>Place of Delivery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KNH</td>
<td>6 (35.2)</td>
<td>7 (26.9)</td>
<td>14 (19.4)</td>
<td>0.3</td>
</tr>
<tr>
<td>Other facility</td>
<td>10 (58.8)</td>
<td>19 (73)</td>
<td>57 (79.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Mode of Delivery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>11 (64.7)</td>
<td>16 (61.5)</td>
<td>50 (69.4)</td>
<td>0.68</td>
</tr>
<tr>
<td>CS</td>
<td>3 (17.6)</td>
<td>8 (30.7)</td>
<td>21 (29.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Maternal Fever</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 (94.1)</td>
<td>23 (88.4)</td>
<td>61 (84.7)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td><strong>Liquor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear liqour</td>
<td>5 (29.4)</td>
<td>10 (38.4)</td>
<td>29 (40.2)</td>
<td>0.7</td>
</tr>
<tr>
<td>Meconium stained liqour</td>
<td>12 (70.5)</td>
<td>16 (61.5)</td>
<td>43 (59.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postpartum hemorrhage</td>
<td>1 (0.05)</td>
<td>2 (0.07)</td>
<td>2 (0.02)</td>
<td>0.03</td>
</tr>
<tr>
<td>Postpartum sepsis</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>5 (100.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of stay</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 24hrs</td>
<td>4 (18.2)</td>
<td>6 (27.3)</td>
<td>11 (50.0)</td>
<td>0.3</td>
</tr>
<tr>
<td>24-48hrs</td>
<td>6 (11.8)</td>
<td>9 (17.6)</td>
<td>32 (62.7)</td>
<td></td>
</tr>
<tr>
<td>&gt;72hrs</td>
<td>6 (15.4)</td>
<td>9 (23.1)</td>
<td>24 (61.5)</td>
<td></td>
</tr>
</tbody>
</table>

Association between Maternal Characteristics and AKI Severity

Table 5 summarizes the association between maternal characteristics and AKI severity. There was no significant association between maternal age, primiparity, marital status level of education, place of delivery and AKI severity. The presence of maternal fever in the week preceding delivery was associated with AKI severity in the neonates p = 0.04. Similarly the
presence of a post-partum complications sepsis and hemorrhage was significantly associated with AKI severity \( p = 0.03 \).

**DISCUSSION**

The KIDGO guidelines define acute kidney injury as an increase in serum creatinine by >0.3mg/dl or >26.5µmol within 48hours or an increase in serum creatinine >1.5 times the base line creatinine levels with urine output of > 0.5ml/kg/hr (23). Diagnosis of AKI is classically dependant on rising serum creatinine and a reduction in urine output.

Our study found an AKI prevalence of 36.1 % (95%CI 31 to 41.6) in neonates admitted with suspected sepsis. These results compare closely with other studies conducted to establish AKI prevalence in neonatal sepsis. Pradan et al in a study in India on AKI and neonatal sepsis found a 27.5% prevalence of AKI in sepsis (35). Vachvanichsanong et al in their study in Thailand found a 30.9% AKI prevalence amongst newborns with sepsis(33). Mathur et al in their study in India found an AKI in sepsis prevalence of 26% (36). These studies used a serum creatinine cut off level of 1.5mg/dl(133µmol/l) for the diagnosis of AKI, unlike in our study where we lowered the serum creatinine cut off level for diagnosis to 100µmol/l after the first 72 hours of life considering that the serum creatinine levels before then reflects maternal serum creatinine levels. This was to improve early diagnosis considering the fact that there is significant loss of renal function by the time the serum creatinine levels rise (1). In addition, the normal serum creatinine level range for neonates is 70 to 80 µmmol/l, so a rise of > 26µmmol/l rounds off to a serum creatinine level of 100µmmol/l as clinically significant.

We further classified the cases based on the RIFLE criteria, 72 of the 120 neonates recruited had failure (62.6%, 95%CI 53.6 to 71.6) followed by injury – 26 (22.6%; 95% CI 14.8 to 30.4) and those under the risk category were 17 (14.8%;95% CI 8.2to21.3). Most of the neonates were in failure and were in need of dialysis and this can be attributed to the fact that KNH is the only referral centre accessible to the public for dialysis. Most of these neonates were received as referrals from facilities within our catchment area. These results are contrary to findings from another study that utilized the RIFLE criteria to classify AKI. Mohkan et al in their study in Tehran-Iran, where they conducted a cohort study of 904 critically ill neonates over a 7 year period and classified the AKI cases into the RIFLE criteria. The AKI
prevalence in their study was 77% with 43% of the neonates in the risk criteria, 51% in the injury category and 6% in the failure category (25).

The assessment of the renal function of the neonates with suspected sepsis revealed that AKI was predominantly non oliguric with the mean urine output at 1.8ml per kg/hour. This finding is consistent with other studies on neonatal AKI (33),(35). This is attributed to the fact that neonates have high total body water as well as immaturity of the nephron’s tubular structure and so they tend have a higher urine output and reduced urine concentrating ability (37).

There were 68 (56.7%) males and 52 (43.3) females of the 120 neonates who presented with AKI during the study period, giving a male to female ratio of 4:3. Bansal et al in a case control study at a level 3 neonatal unit in India found that the male gender and sepsis were the only demographic variables that had a significant association with AKI. The male gender had an odds ratio of (OR=2.84) (CI=1.12-7.21) and sepsis odds ratio of (OR=14.6) (CI 4.5-46.46) (38). Similarly, Youssef et al in a prospective study conducted at a NICU at a children’s hospital in Egypt found an AKI prevalence of 10.8%, male sex predominance with the male to female ratio of 1.3:1. In this study sepsis was also found to be the leading predisposing factor to developing AKI at 63% (39).

There was a significant association between AKI and the age of the neonates in our study (ANOVA p=0.04). There were 29 neonates (24%) aged 0-7 days who developed AKI and 89 (75.4%) neonates aged more than 7 days. Neonates classified as having AKI risk were on average aged 8.3 days compared to those with injury (mean = 12.8 days ± 7.1) and those in failure (mean = 11.2 days ± 5.2). Post-hoc analysis showed that the difference in age between neonates at risk and those with injury was statistically significant while that between injury and failure or risk and failure was not significant. Mean gestational age (p = 0.823) and birth weight (p = 0.767) were not significantly associated with AKI. Holda et al in their study in India on the effects of neonatal septicaemia on renal function found that AKI occurred more frequently in neonates who had early onset neonatal sepsis at 54.8% and 45.2% for late onset sepsis contrasting the results from our study(10).

The maternal demographic factors under investigation were found to have no significant association with AKI in the neonates with suspected sepsis. Primi parity was associated with the highest number of the AKI cases at 72 (60%) p=0.071. Most of these neonates were in the failure category at 61.1%. Similarly, the presence of maternal fever within a week of delivery was found to be associated with AKI with 100 (80%) p=0.065. Both primi parity and
maternal fever in the peripartum period are risk factors for neonatal sepsis (41), rather than direct risk factors for AKI attributable to sepsis. This findings are similar to those found in a study by Cataldi et al in their study in Italy on potential risks for acute renal failure in preterm neonates found that peripartum sepsis and exposure to antibiotics in the immediate peripartum period were significantly associated with AKI (p=0.004). Similarly, in this study, primiparity was not significantly associated with AKI (p=0.78) (42).

**STUDY STRENGTHS**

The study site has clinical guidelines on management of common neonatal conditions practiced by all residents directly involved in the care of the sick neonates. This facilitated timely collection of blood samples, catheterization and reduced variations in the overall quality of care received by the study population.

The principal investigator and assistants were able to follow up the recruited cases over a 24 hour period to ascertain urine output and this gave an opportunity to evaluate the study subjects conclusively and minimized information errors during the data collection process.

Our results are generalisable to other centers attending to sick term newborns.

**STUDY LIMITATIONS**

The study was unable to generate correlates on risk factors as it was not feasible within our time frame and budget to have a comparative arm of neonates with suspected sepsis but without AKI to be able to determine whether the risk factors under investigation had a true causal association.

**CONCLUSION**

36% of neonates admitted with suspected sepsis is likely to develop AKI. The severity of AKI in terms of the RIFLE criteria correlates with the severity of sepsis. Neonates with late onset neonatal sepsis are twice more likely to develop AKI than those with early onset neonatal sepsis. Male neonates are 2 times more likely to develop AKI than their female counterparts.
RECOMMENDATIONS

- Clinicians should screen for AKI in all neonates with suspected sepsis by assessment of serum creatinine levels at the earliest opportunity. This will pave way for timely interventions to preserve kidney function.

- Further studies on neonatal AKI are required to establish outcomes considering the fact that the majority of the neonates with AKI had the severe form of AKI and to evaluate the quality of care offered to these neonates.

- Mothers who suffer peripartum sepsis and post partum hemorrhage should have their neonates evaluated for sepsis and likely kidney dysfunction as a complication.
REFERENCES


38. EBSCOhost | 121528931 | Clinical Profile and Outcome of Newborns with Acute Kidney Injury in a Level 3 Neonatal Unit in Western India. [Internet]. [cited 2017 Apr 11].
**APPENDICES**

**Appendix I: Observation Checklist for Suspected Sepsis**

<table>
<thead>
<tr>
<th>Vitals</th>
<th>Temperature °C</th>
<th>Respiratory rate b/min</th>
<th>Pulse rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Examination</td>
<td>Lethargic</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>Unable to feed</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>Pallor</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>Cyanosis</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>Cold extremities</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Nasal flaring</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>Grunting</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>Lower chest wall in drawing</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Capillary refill time</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heart rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS*</td>
<td>Level of consciousness</td>
<td>AVPU</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bulging fontanelle</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>Convulsions</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Local Signs of Sepsis</td>
<td>Periumbilical flare</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>Pus discharge from umbilicus</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>Skin pustules</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>discharging eyes</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

Registration number:

*CNS: Central Nervous System examination, level of consciousness will be documented as Alert, response to Voice, Pain or Unconscious.(AVPU).
Appendix II: Study Questionnaire for Prevalence of Acute Kidney Injury and its Associated Risk Factors in Neonates with Suspected Sepsis

<table>
<thead>
<tr>
<th>1.0 Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Questionnaire Serial No.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2.0 Personal details</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2 Current age (in days)</td>
</tr>
<tr>
<td>Age at diagnosis (in days)</td>
</tr>
<tr>
<td>2.4 Estimated gestation at birth in weeks</td>
</tr>
<tr>
<td>2.5 Birth Weight in grams</td>
</tr>
<tr>
<td>2.6 Birth order</td>
</tr>
<tr>
<td>2.7 Documented urine output over 24hrs</td>
</tr>
<tr>
<td>2.8 Serum creatinine levels in µmol/l</td>
</tr>
<tr>
<td>2.9 Neonatal RIFLE CLASSIFICATION Risk Injury Failure Loss</td>
</tr>
</tbody>
</table>
3.0 Mother’s Data

<table>
<thead>
<tr>
<th>Section</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1 Age (in completed years)</td>
<td>[ ] Don’t know [<strong>]-[</strong>]-[__]</td>
</tr>
<tr>
<td>3.3 Parity</td>
<td>[ ]Primi parity [ ]Multi parity</td>
</tr>
<tr>
<td>3.7 Antenatal Clinic visits</td>
<td>[ ] Don’t know [0] No [1] Yes</td>
</tr>
<tr>
<td>4.1 Maternal fever (within one week before delivery)</td>
<td>[ ] Don’t know [0] No fever [1] Fever</td>
</tr>
<tr>
<td>4.2 Duration of labour (in hours)</td>
<td>[ ] Don’t know [__]</td>
</tr>
<tr>
<td>4.3 Duration of rupture of membranes (in hours)</td>
<td>[ ] Not known [__]</td>
</tr>
<tr>
<td>4.4 Amniotic fluid colour</td>
<td>[ ] Not known [0] Green [1] Clear</td>
</tr>
<tr>
<td>History of urinary tract infection during pregnancy</td>
<td>[0] No [1] Yes</td>
</tr>
<tr>
<td>4.5 postpartum complications</td>
<td>[0] No [1] Yes</td>
</tr>
<tr>
<td>If yes at 4.5 which one</td>
<td>Postpartum hemorrhage</td>
</tr>
<tr>
<td>Post-partum sepsis</td>
<td></td>
</tr>
</tbody>
</table>

4.6 Duration of hospital stay post-partum. (1) less than 24hrs (2) 24-48hrs (3) >72hrs
Appendix III: Consent Form for Parents / Guardians of Participants

<table>
<thead>
<tr>
<th>Title</th>
<th>Prevalence of Acute Kidney Injury and its associated Risk Factors in Neonates with Suspected Sepsis admitted to Kenyatta National Hospital.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scope</td>
<td>This informed consent form is for enrolled participants in the study and will be read to them by a qualified research assistant before answering the questions.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serial No.</th>
<th>Date</th>
<th>Site</th>
<th>KNH Pediatric Wards</th>
</tr>
</thead>
</table>

Investigator: Dr. Catherine Munyendo

Tel: 0721-217824

Email: cathymunyendo@gmail.com

Sponsor: KNH

This informed consent form has two parts:

- Information sheet (to share information about the study with you)
- Certificate of Consent (for signatures if you choose to participate)

Part 1: Information Sheet

Introduction

We are inviting you to participate in this study to determine the prevalence of acute kidney injury in neonates with suspected sepsis admitted to the pediatric wards in Kenyatta National Hospital.

Neonatal sepsis is the commonest problem encountered in newborns at the time of admission. It is a condition caused by bacterial infections to the newborn that causes them to have fever and refuse to feed and can complicate to damage their organs. The kidneys are often damage by the effects of the infection on its blood supply and the dehydration that ensues due to poor feeding during the illness.
This study intends to establish the magnitude of the problem so as to sensitize health care workers and the parents/caregivers for early detection and prompt management of cases to prevent the long term complications associated with kidney disease.

You do not have to make the decision solely on whether to participate in the study; feel free to seek the opinion of those you trust before you can get to consent.

The form may contain words that you may not understand, kindly seek clarification from the research assistant as you go along and they will take time to explain and you can contact the investigator at any time via the mobile number availed should you have any questions not answered to your satisfaction.

**Purpose of the Study**

The study primarily aims to determine the prevalence of acute kidney injury and its associated risk factors in neonates with suspected sepsis admitted to Kenyatta National Hospital level three pediatric wards. The information will help us make certain decisions that will help in the care of these newborns.

**Procedures**

You will be offered a questionnaire to which you can respond to yourself in writing or you can speak out your answer clearly for the investigator or assistant to write it down. If you do not feel like responding to any of the questions included you are allowed to skip them and proceed to those questions that you feel comfortable to respond to. This interview is expected to last 20 minutes. The information obtained is confidential and your name will not appear in any of the forms; only a number code will be used to identify you and no one else other than the research investigators will access the information you have provided.

At the time of admission, a blood sample to assess the kidney function of your newborn will be obtained. The amount of urine passed by the newborn in 12 hours from the time of admission will be determined by urine collection bags or by a way of urethral catheter with a urine bag which will only be inserted with your permission.

**Risks:** We are asking you personal and sensitive information and you may not feel comfortable to disclose. Only respond to questions that you are comfortable with and you do not need to explain why you have chosen not to answer any question.
Benefits: In future you and other mothers will benefit from improved quality of services provided in the pediatric wards as a result of the findings of this study.

Confidentiality: We will keep all the information about you in utmost confidentiality. We will not share it with anyone outside the research team. No names will appear on the research tools; number codes will be used at all times. Only the research team will know what your number code is and all the research paper work will be under our safe custody.

Sharing results: None of the information collected from you today will be shared with anyone outside the research team. The knowledge obtained as a result of this study will be shared with you and other parents and caregivers in the pediatric wards in KNH before the information is made public. Each participant will receive a summary of the results and we intend to publish the results for other interested persons to learn from the study.

Who to contact: Your consent form has the contact of the principal investigator. Feel free to get in touch with her anytime.

This proposal will be reviewed by the Kenyatta National Hospital/University of Nairobi Ethics and Review Committee to ensure that the study participants are protected from harm.

If you wish to find out more about the Ethics and Review Committee contact:

The Chairman,
Kenyatta National hospital/ University of Nairobi Ethic and Review Committee
P.O. Box 20723
Nairobi, Kenya.

PART 2: Certificate of Consent

I have read the above information / the above information has been read to me. I have had an opportunity to ask questions and they have been satisfactorily answered. I consent voluntarily to be a participant in this study.

Print the name of the participant: __________________________________________

Signature of participant: ________________________________

Date: ___/___/____ dd/mm/yy
If Illiterate: I have witnessed the accurate reading of the consent form to the participant and the individual has had the opportunity to ask questions.

I confirm that the individual has given consent freely.

__________________________________________________________________
Print the name of the witness
Signature of witness  ……………………………..

Thumb print of participant

Date: ___/___/___  dd/mm/yy

Statement by the Researcher or the person taking Consent

I …………………………………………………………………………………………… have accurately read out the information sheet to the potential participant, and, to the best of my ability, I have explained the study procedure, the benefits and the risks, and given him/her time to ask questions and seek clarification regarding the study. I have answered all the questions raised to the best of my ability.

Signature of researcher: …………………………………

Date: ………………………
Fomu ya Kupata Kibali cha Wazazi/Walezi wa Washiriki

Utangulizi

Hii fomu ya kupata idhini ni kwa ajili ya watoto waliolazwa katika hospitali ya kitaifa ya Kenyatta, ambao tunawakaribisha kushiriki katika utafiti. Mradi wetu wa utafiti ni kuhusu, “Ufanisi wa magonjwa ya kuambukizana na athari zake kwa figo za watoto wachanga walio chini ya mwezi mmoja na wasiopungua uzito wa kilo mbili.”

Mimi ni Daktari Catherine Munyendo, mwanafunzi katika Chuo Kikuu cha Nairobi. Ninashiriki masomo ya utaalamu wa afya ya watoto. Ninafanya utafiti huu kama sehemu kuu ya masomo yangu nikikusudia ya kwamba matopeo yatakayotokana na utafiti huu yataboresha utendaji kazi na matibabu ya watoto wenye magonjwa ya maambukizi ya figo.

Kunaweza kuwa na baadhhi ya maneno ambayo hauelewi; tafadhali uliza nami nitachukua fursa kukueleza. Ukiwa na maswali pia baadaye una waielewa kwenye utafiti huu.

Sababu ya Utafiti

Magonjwa ya maambukizi yanaweza kusababisha madhara mengi katika viungo vya watoto wachanga ambao wipelewa mbili wangu. Utuaji kwa mawazo mbili wako, kwa kugawanya mawazo yako baadaye una waielewa kwenye utafiti huu.

Maandalizi ya Utafiti

Utafiti huu utahusisha upimaji wa damu wa umri na mwezi wa kubali wa kutoka kwa utafiti. Utuaji kwa njia yake ni kwa mwezi wa mawazo mbili wa kufaraha kwa watoto wachanga ambao wamekufurahia na kuwagawanya mawazo mbili wa kutoka kwa utafiti kwa mwezi wa mawazo mbili wa kufaraha.
Madhara

Utafiti huu hautamdhuru mwanao kwa vyovyote vile. Ukiwa na tashwishi yoyote kuhusu matibabu ya mwanao, uko huru kuuliza maswali ili uelezewe kikamilifu.

Habari zozote ambazo utatueleza kutokana na mradi huu zitawekwa siri na hatutamjulisha yeystote bila idhini yako.

Mawasiliano

Kama una maswali yoyote unaweza kuuliza hivi sasa au baadaye, ama wakati wowote unapojaadiliana nami. Pia waweza wasiliana nami kwa nambari 0721 217824.

Nimesoma / nimesomewa maelezo haya na nimepewa nafasi ya kuuliza maswali hivi sasa na baadaye kuhusu utafiti huu. Nimeidhinisha kwa hiari yangu binafsi kushiriki katika utafiti huu.

Jina la Mshiriki: ………………………………………………………………………………………………………

Sahihi ya Mshiriki: ………………………

Tarehe: ……………………………

Taarifa ya Mtafiti ama anayepata ruhusa ya Mshiriki

Nina uhakika kuwa nimemsomea mwakilishi fomu hii na kwa kadri ya uwezo wangu, nimehakikisha kwamba mshiriki ameelewana.

Ninathibitisha ya kuwa mshiriki alipewa nafasi ya kuuliza maswali kuhusu utafiti na kadri ya uwezo wangu niliyajibu maswali hayo. Pia, ninathibitisha kuwa mshiriki hakulazimishwa kutoa kibali cha kushiriki.

Jina la Mtafiti: ………………………………………………………………………………………………………

Sahihi ya Mtafiti: ………………………

Tarehe: ……………………………
Appendix IV: Procedure for Urethral Catheterisation (47)

- The procedure will be explained to the mother/care giver to obtain their consent
- The neonate will then be placed into the appropriate supine position.
- Hand washing and wearing of the disposable apron will then be put on
- Sterile gloves will then be worn.
- A sterile drape will be placed beneath the baby’s buttocks to create a sterile field.
- A sterile pack and 0.9% saline solution will be used for genital cleansing before the procedure.
  - **For male babies**, a gauze swab will be wrapped around the penis to retract the foreskin if necessary. Then cleaning will be done with sterile gauzes soaked in 0.9% saline with single strokes away from the meatus.
  - The gloves will then be changed.
  - The penis will then be held in extension and the foreskin may then be gently retracted.
  - The pre-connected catheter and urine bag will then be placed on the sterile field.
  - Then holding the catheter through the packaging the catheter will be inserted gently using a slow steady pressure until when urine will be seen to flow out.
  - **For female patients**, a sterile gauze swab will be used to separate the labia minora to visualize the urethral meatus. Then cleaning with swabs soaked in 0.9% sodium chloride solution using single downward strokes away from the meatus (front to back) is done.
  - Then the gloves will be changed.
  - The pre-connected catheter bag will be placed on the sterile field.
  - Then, holding the catheter through the packaging, it will be gently inserted using a slow steady pressure, into the meatus, upward at ~ 30° angle until urine flows.
  - The catheter balloon will then be slowly inflated using the syringe of sterile water while the patient will be observed for discomfort.
  - The catheter will then be drawn out gently.
  - The sterile field will then be removed.
  - In preparation for stabilizing the catheter the leg will be fully extended and the catheter will be positioned straight on the front of the thigh. Then the catheter will be backed up a couple of centimeters to create some slack and it will be secured on the thigh.
  - The catheter bag will then be positioned below the bladder on a stand ensuring that the drainage port is not in contact with the floor.
  - The residual urine amount will be measured and the procedure notes documented in the patients file.
## Appendix V: Neonatal RIFLE Criteria (24)

<table>
<thead>
<tr>
<th>Neonatal RIFLE</th>
<th>Serum Creatinine</th>
<th>Urine Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>Increased Scr×1.5 or GFR &gt;25%</td>
<td>UO &gt; 1.5 ml/kg/hr</td>
</tr>
<tr>
<td>Injury</td>
<td>Increased Scr×2 or GFR decrease by &gt;50%</td>
<td>UO &lt; 1 ml/kg/hr</td>
</tr>
<tr>
<td>Failure</td>
<td>Increased Scr×3 or GFR decrease by &gt;75%</td>
<td>UO &lt; 0.5 ml/kg/hr</td>
</tr>
<tr>
<td>Loss</td>
<td>Persistent failure for &gt;4 weeks</td>
<td></td>
</tr>
<tr>
<td>End stage disease</td>
<td>End stage renal disease for more &gt;3 months</td>
<td></td>
</tr>
</tbody>
</table>
### Appendix VI: Study Budget

<table>
<thead>
<tr>
<th>Category</th>
<th>Remarks</th>
<th>Units</th>
<th>Unit Cost (KShs)</th>
<th>Total (KShs)</th>
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</thead>
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<td></td>
<td>Proposal Copies</td>
<td>8 copies</td>
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<td>4,000</td>
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<tr>
<td>Data Collection</td>
<td>Stationery packs (pens, paper and Study Definitions)</td>
<td>10</td>
<td>100</td>
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<td></td>
<td>Training Research Assistants</td>
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<td>1,000</td>
</tr>
<tr>
<td></td>
<td>Research assistants (2)</td>
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<td>1,000 × 2</td>
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</tr>
<tr>
<td>Equipment</td>
<td>Pediatric urinary catheters</td>
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<td>Data Analysis</td>
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<tr>
<td>Contingency funds</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>94,000</strong></td>
</tr>
</tbody>
</table>
Ref: KNH-ERC/1A/257

Dr. Catherine Munyendo  
Reg. No. H58/75545/2014  
Dept. of Paediatrics and Child Health  
School of Medicine  
College of Health Sciences  
University of Nairobi

Dear Dr. Munyendo,

REVISED RESEARCH PROPOSAL: PREVALENCE OF ACUTE KIDNEY INJURY AND ITS ASSOCIATED RISK FACTORS IN NEONATES WITH SUSPECTED SEPSIS ADMITTED TO KENYATTA NATIONAL HOSPITAL (P270/02/2016)

This is to inform you that the KNH-UoN Ethics & Research Committee (KNH-UoN ERC) has reviewed and approved your above proposal. The approval period is from 13th July 2016 – 12th July 2017.

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 serious 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 ERC 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.

"Protect to discover"
For more details consult the KNH-UoN ERC website http://www.erc.uonbi.ac.ke

Yours sincerely,

PROF. M.C. CHINDIA
SECRETARY, KNH-UoN ERC

C.c.
- The Principal, College of Health Sciences, UoN
- The Deputy Director, CS, KNH
- The Assistant Director, Health Information, KNH
- The Chair, KNH-UoN ERC
- The Dean, School of Medicine, UoN
- The Chair, Dept. of Paediatrics and Child Health, UoN
- Supervisors: Dr. Bashir A., Dr. Laving A., Dr. Gachara N.

"Protect to discover"
# Prevalence of Acute Kidney Injury and Its Risk Factors for Severity in Neonates with Suspected Sepsis at Kenyatta National Hospital

**Originality Report**

<table>
<thead>
<tr>
<th>Similarity Index</th>
<th>Internet Sources</th>
<th>Publications</th>
<th>Student Papers</th>
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<tr>
<td>10%</td>
<td>5%</td>
<td>8%</td>
<td>3%</td>
</tr>
</tbody>
</table>

**Primary Sources**

1. **www.pubfacts.com**
   - Internet Source
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   - Internet Source
   - 1%

   - Publication
   - 1%

   - Publication
   - 1%

   - Publication
   - <1%

6. Submitted to Higher Education Commission Pakistan
   - <1%