Prevalence, associated factors and early clinical outcome of acute kidney injury among critically ill neonates admitted at Muhimbili National Hospital, Dar es salaam

Naomi Amon Mwamanenge, MD

MMed (Pediatrics and Child Health) Dissertation
Muhimbili University ealth and Allied Sciences
October, 2018

Muhimbili University of Health and Allied Sciences

Department of Pediatrics and Child Health

PREVALENCE, ASSOCIATED FACTORS AND EARLY CLINICAL OUTCOMEA OF CUTE KIDNEY INJURY AMONG CRITICALLY ILL NEONATES ADMITTED AT MUHIMBILI NATIONAL HOSPITAL, DAR ES SALAAM

By

Naomi Amon Mwamanenge

A Dissertation Submitted in (Partial) Fulfillment of the Requirements for the Degree of Master of Medicine (Paediatrics and Child Health) of

Muhimbili University of Health and Allied Sciences
October, 2018

CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled**: "Prevalence, associated factors and early clinical outcome of Acute kidney injury among critically ill neonates admitted at Muhimbili National Hospital, Dar es salaam, Tanzania",** in (partial) fulfillment of the requirements for the degree of Master of Medicine (Paediatrics and Child Health) of the Muhimbili University of Health and Allied Sciences.

_____

Dr. E. Assenga

Supervisor 1

_____

Date

_____

Dr. F. Furia

(Supervisor 2)

_____

Date

DECLARATION AND COPYRIGHT

I, **Dr**. **Naomi A. Mwamanenge**, hereby declare that this **dissertation** is my own original work and that it has not been presented and shall not be presented to any other university for a similar or any other degree award.

Signature…… **Date**……

This dissertation is a copyright material protected under the Berne Convention, the Copyright Act 1999 and other international and national enactments, in that behalf, on intellectual property. It may not be reproduced by any means, in full or in part, except for short extracts in fair dealing, for research or private study, critical scholarly review or discourse with an acknowledgement, without the written permission of the Directorate of Postgraduate Studies, on behalf of both the author and the Muhimbili University of Health and Allied Sciences.

AKNOWLEDGEMENTS

Firstly I would like to thank my supervisors Dr. Evelyne Assenga and Dr. Francis Furia for their guidance, contributions and support throughout this study period.

Special thanks go to Dr .Amon Sabasaba for his expertise guidance in design and analysis and my research assistant Dr. Rodrick Lwamayanga.

I would like also to extend my appreciations to Muhimbili National Hospital for giving me permission to conduct research in the neonatal ward including the head of department of neonatal ward Dr. Edna Majaliwa, other staff members and parents of the study participants for agreeing to take part in this study.

In addition I thank the department of Pediatrics and Child Health of Muhimbili University of Health and Allied Sciences for their constructive inputs throughout my training and dissertation work.

Lastly I thank deeply my lovely parents, Mr. and Mrs A. Mwamanenge and my siblings Herymaria, Aliko with his wife Gladys, Sayuni Bupe and Daniel with his wife Judith for their continual support and encouragement throughout the course.

DEDICATION

This work is dedicated to my parents and my siblings.

ABSTRACT

Background

Acute kidney injury (AKI) is an emerging public health problem globally; the burden of this condition in sub-Saharan Africa is not well documented particularly for neonates, infants, and children. Causes of AKI in neonates are several and include sepsis, and birth asphyxia; these are the leading causes of neonatal mortality globally. Critically ill neonates are at increased risk for AKI and timely diagnosis and management is crucial for their survival.

Objectives

To determine the prevalence, factors associated and early clinical outcome of AKI among critically ill neonates admitted at the Muhimbili National Hospital (MNH), Dar es Salaam.

Methodology

This was a cross-sectional study conducted at the MNH neonatal unit. Participants included critically ill neonates admitted from October 2017 to March 2018**.** Critically ill neonates were recruited consecutively. Data was collected using a standardized structured questionnaire. Blood samples were drawn for measuring serum creatinine (SCr) at admission, at the 72nd hour and at the 14th day.

Data was analyzed using SPSS version 20.0 Univariate analysis was done using chi-square to determine the association between the different associated factors and AKI. Multivariate logistic regression was then used to determine the association between AKI and known associated factors found to be significant on univariate analysis. A p value of less than 0.05 was considered statistically significant.

Results

A total of 378 critically ill neonates were enrolled with predominance of males 59.8% (226 participants). The median age (Inter-Quartile Range) at admission was 3 (1, 6) days. The prevalence of AKI was 31.5%. Independent predictors of AKI were neonatal sepsis (aOR 2.237, 95%CI 1.3-3.6, P=0.001), severe pneumonia (aOR3.0, 95%CI 1.0-9.3, P=0.047) and usage of gentamycin (aOR6.8, 95%CI 1.3-9.3, P=0.02). Complete resolution of renal

dysfunction at the fourteenth day was seen in 83.1% while 16.9% had persistence of renal dysfunction. Participants with AKI were noted to have significantly higher mortality 70.6% as compared to those without AKI 29.4% p-value of 0.000

Conclusion and Recommendations

AKI is prevalent in critically ill neonates and has a high mortality rate. Early detection and management is critical in order to alleviate the morbidity and mortality associated with AKI.

MUHSTASARI

Utangulizi:

Maradhi makali ya figo kwa watoto chini ya umri wa siku ishirini na nane baada ya kuzaliwa ni suala ambalo linaibuka japo kuna uhaba wa taarifa zinazohusu ukubwa wake. Katika eneo letu,haya maradhi makali ya figo yana visababishi/vyanzo tofauti katika kundi la watoto chini ya siku 28. Ni muhimu kuhakikisha uangalizi na uchunguzi bora ambao utapunguza ugonjwa huu na vifo.

Maudhui:

Utafiti huu ulikuwa na lengo la kutambua ukubwa na visababishi hatarishi vya maradhi makali ya figo kwa watoto wachanga walio mahututi waliolazwa katika hospitali kuu ya Taifa, Muhimbili, Dar es Salaam.

Mbinu:

Utafiti huu ulifanyika kwa watoto walio mahututi waliolazwa katika jengo la watoto kwenye hospitali kuu ya Taifa, Muhimbili kati ya oktoba 2017 na machi 2018.Watoto waliokidhi vigezo vya kushiriki waliingizwa kwenye utafiti kadri walivyokuwa wakipatikana hadi idadi ilivyotimia. Dodoso ilitumika kukusanya taarifa binafsi. Damu ilichukuliwa kwa ajili ya kupima “serum creatinine” wakati wa kulazwa na baada ya masaa 72 na ya siku 14.

Matokeo:

Utafiti huu ulihusisha watoto 378, wengi wao walikuwa watoto wakiume 59.8% (226). Watoto walilazwa wakiwa na wastani wa umri wa siku 3 (1- 6). Maradhi makali ya figo yalipatikana kwa asilimia 31.5% (119). Visababishi hatarishi vilikuwa “neonatal sepsis” (aOR 2.237, 95%CI 1.3-3.6, P=0.001), homa kali ya mapafu (aOR3.0, 95%CI 1.0-9.3, P=0.047) na utumiaji wa dawa “gentamycin” (aOR6.8, 95%CI 1.3-9.3, P=0.02). Asilimia 83.1(49) walipona wakati asilimia 16.9(10) waliendelea kulazwa kwa sababu “serum creatinine” ilikuwa bado ipo juu. Vifo vilikuwa wingi kwa watoto walio na maradhi hayo kwa asilimia 70.6 (60) wakati wale ambao walikuwa hawana walikuwa asilimia 29.4(25) p-value 0.000.

Hitimisho:

Watoto wachanga mahututi hupata maradhi makali ya figo kwa asilimia 31.5% hivyo ni vyema kuwafuatilia kwa karibu ili kuwagundua mapema na kuwapa tiba sahihi.

TABLE OF CONTENTS

CERTIFICATION i
DECLARATION AND COPYRIGHT ii
AKNOWLEDGEMENTS iii
DEDICATION iv
ABSTRACT v
MUHSTASARI vii
TABLE OF CONTENTS ix
LIST OF TABLES xii
LIST OF FIGURES xiii
LIST OF ABBREVIATIONS xiv
OPERATIONAL DEFINITIONS xv
1.0 INTRODUCTION 1
1.1 Problem Statement 3
1.2 Rationale 3
1.3 Conceptual Framework 4
1.4 Research Questions 5
1.5 Objectives 6
1.5.1 Broad objective 6
1.5.2 Specific objectives 6
2.0 LITERATURE REVIEW 7
2.1 Neonatal renal transition 7
2.2 Neonatal renal functions 7
2.3 Prevalence Acute kidney injury in neonates 8
2.4 Factors associated with AKI 8
2.4.2 Prematurity 9
2.4.3 Sepsis 10
2.4.5 Drug-induced nephrotoxicity 10
2.4.6 Other factors 11

2.5 Outcome of neonatal acute kidney injury 11
2.5.1 Resolution of kidney functions 11
2.5.2 Morbidity and mortality 12
3.0 METHODOLOGY 13
3.1 Study design 13
3.2 Study setting 13
3.3 Study population 13
3.4 Sample size 13
3.5 Sampling procedure 14
3.6 Inclusion criteria 14
3.7 Exclusion criteria 14
3.8 Data collection 14
3.9 Data management and analysis 15
3.10 Pre-testing of the study tool 16
3.11 Ethical Consideration 16
4.0 RESULTS 17
4.1 Social-demographic characteristics of the study participants 17
4.2 Prevalence of AKI among critically ill neonates 18
4.3 Trend of serum creatinine 18
4.4 Factors associated with AKI 19
4.5 Multivariate logistic regression 21
4.6 Ultrasound findings of participants with AKI 22
4.7 Outcome for patients with AKI 22
4.8 Resolution of renal functions 23
5.0 DISCUSSION 24
5.1 Prevalence 24
5.2 Factors associated with acute kidney injury 24
5.3 Outcome 26
5.4 Strength 27

6.0 CONCLUSION AND RECOMMENDATION 28
6.1 Conclusion 28
6.2 Recommendation 28
REFERENCES 29
APPENDICES 34
Appendix I: Questionnaire 34
Appendix II: Consent Form – English 37
Appendix III: Fomu Ya Ridhaa Kwa Mzazi 39

LIST OF TABLES

Table 1: Socio-Demographic characteristics of the study participants……17

Table 2: Factors associated with AKI …….20

Table 3: Logistic regression on risk factors for AKI ……..21

Table 4: Outcome for patients with AKI……..23

Table 5: Resolution of renal dysfunction in patients with AKI ……..….23

LIST OF FIGURES

Figure 1: Conceptual Framework……....4

Figure 2: Pie chart showing proportion of Acute Kidney Injury (AKI) among studied Critically Ill Neonates admitted at MNH……..18

Figure 3: Trend of SCr baseline and follow up of the 378 studied participants……19

Figure 4: Bar graph showing proportion of KUB findings in those with AKI……..22

LIST OF ABBREVIATIONS

AKI	Acute Kidney Injury
AKIN	Acute Kidney Injury Network
ANC	Antenatal Clinic
APGAR	Appearance, Pulse, Grimace, Activity, Respiration
CHD	Congenital heart disease
GA	Gestational Age
GFR	Glomerular Filtration Rate
HIE	Hypoxic Ischemic Encephalopathy
KDIGO	Kidney Disease Improving Global Outcome
KUB	Kidney urinary bladder
MNH	Muhimbili National Hospital
MUHAS	Muhimbili University of Health and Allied Sciences
PD	Peritoneal Dialysis
pRIFLE	Pediatric Risk, Injury, Failure, Loss, And End-Stage Renal Disease
RRT	Renal Replacement Therapy Includes PD, Hemodialysis
Scr	Serum Creatinine
UO	Urine Output
WHO	World Health Organization

OPERATIONAL DEFINITIONS

For the purpose of this study the following definitions were used:

Neonates: is a newborn infant less than 28 days of life. (1)

Premature: is all birth before 37 weeks of completed gestational age.(1)

Acute kidney injury: is an increase in serum creatinine of more or equal to 26 micromol/l from baseline in 48 hours or an increase in serum creatinine to 1.5 times baseline, which is known or presumed to have occurred within the prior seven days.(2)

Critically ill neonates: were defined as all neonates admitted in the ward with signs of severe illness, which included vomiting everything, lethargy, convulsions, hypo/hyperthermia, poor feeding, jaundice, respiratory distress, dehydration or shock and decreased urine output.

Recovery was defined as return to normal of the renal functions in those who had AKI.

APGAR a cut off of ≤ 6 was used for severe and moderate HIE while ≥ 7 as normal apgar score (29)

1.0 INTRODUCTION

Acute kidney injury (AKI) in neonates is defined as a reversible increase in the concentration of serum creatinine (SCr) and nitrogenous waste products and the inability of the kidney to regulate fluid and electrolyte homeostasis. (3) AKI is reported to be common among critically ill patients and is usually underdiagnosed because of several factors including poor knowledge, lack of facilities for laboratory tests, and lack of its awareness. In sub -Saharan Africa, kidney injury has been reported to be as high as 33.3% amongst neonates in a Zimbabwean study done in 2013. (4)

Newborn with genito-urinary malformation are at increased risk of developing AKI and chronic kidney disease (CKD) in adulthood.(5–7) A study done by Carmody *et al* in 2013 showed that preterm and low birth weight (LBW) neonates were at higher risk of developing CKD due to reduced glomeruli number. (8)

AKI is diagnosed based on serum creatinine (SCr) and urine output quantification. Earlier studies used a SCr more than 133µmol/L for the detection of AKI however this made those with initial stages of AKI to be missed. Studies show that even small changes in SCr are associated with increased morbidity and mortality hence to better define and detect AKI early, newer empirical definitions were set including RIFLE, AKIN and KDIGO. (9) In 2014, a multinational retrospective cohort study was done in which KDIGO-AKI definition was validated in order to detect AKI in the neonates. (2,10)

The KDIGO Classification is as follows (10)

Stage	Serum creatinine	Urine output
1	≥26.5 µmol/l increase within 48hours or 1.5-1.9 times baseline which is known or presumed to have occurred within the prior seven days	≤0.5ml/kg/hr for 6-12 hours
2	2.0-2.9 times the baseline	≤ 0.5ml/kg/hour for 12hours
3	≥ 353.6 µmol/l or 3.0 times baseline or initiation of renal replacement therapy	≤ 0.3ml/kg/hour

The management of AKI is variable. It requires knowledge about the correct dosing of renal sensitive medications, and the correct fluid administration. (11) Early detection of AKI ensures timely management which include removal of nephrotoxic drugs and treatment of underlying conditions, this may curtail the need for renal replacement therapy which is indicated with severe AKI. Timely detection and management of AKI is crucial for preventing prolonged hospital stay and mortality. (12)

1.1 Problem Statement

Acute kidney injury is a common complication seen in critically ill neonates. (3) Its early diagnosis and intervention can affect morbidity and mortality. The manifestation of AKI can be mild or severe leading to end stage renal failure. Neonates who survived an episode of AKI or those who have persistent of renal dysfunction may develop chronic kidney disease (CKD) in the long run. Studies have shown that the incidence of AKI is variable amongst neonates ranging from 2.8% to as high as 36.6% depending on the underlying associated factors. (13,14) This is contributed by the immaturity of the newborn kidney, gradual physiologic transition, its adaptive capabilities during stress and presence of congenital renal anomalies.

In developing countries like Tanzania, there is limited data on the prevalence of kidney dysfunction amongst neonates. This can be attributed to lack of analytical documentation of these cases, and hence there is no database showing the burden of kidney dysfunction in neonates in our setting.

1.2 Rationale

Findings from this study will help to alert physicians to the need for early diagnosis and management of AKI in neonates. Importantly, the study also brings to the attention of practitioners the need to exercise precaution to ensure renal safe treatment for all critically ill neonates with AKI. In addition, a database on renal injury in neonates has now been developed which will facilitate long-term follow up and linkage with the pediatric nephrology department so that such cases are not lost to follow up.

1.3 Conceptual Framework

Disturbance in the renal functions can be brought about by prerenal causes such as sepsis, renal causes such as HIE, and congenital anomalies of the kidney and urinary tract such as PUV. With early diagnosis and intervention, these disturbances can either normalize resulting in full recovery or can lead to extended hospital stay while allowing renal functions to return to normal. However, late diagnosis or failure to detect AKI can result in poor management including the use of nephrotoxic drugs which can lead to prolonged morbidity, mortality or long-term CKD.

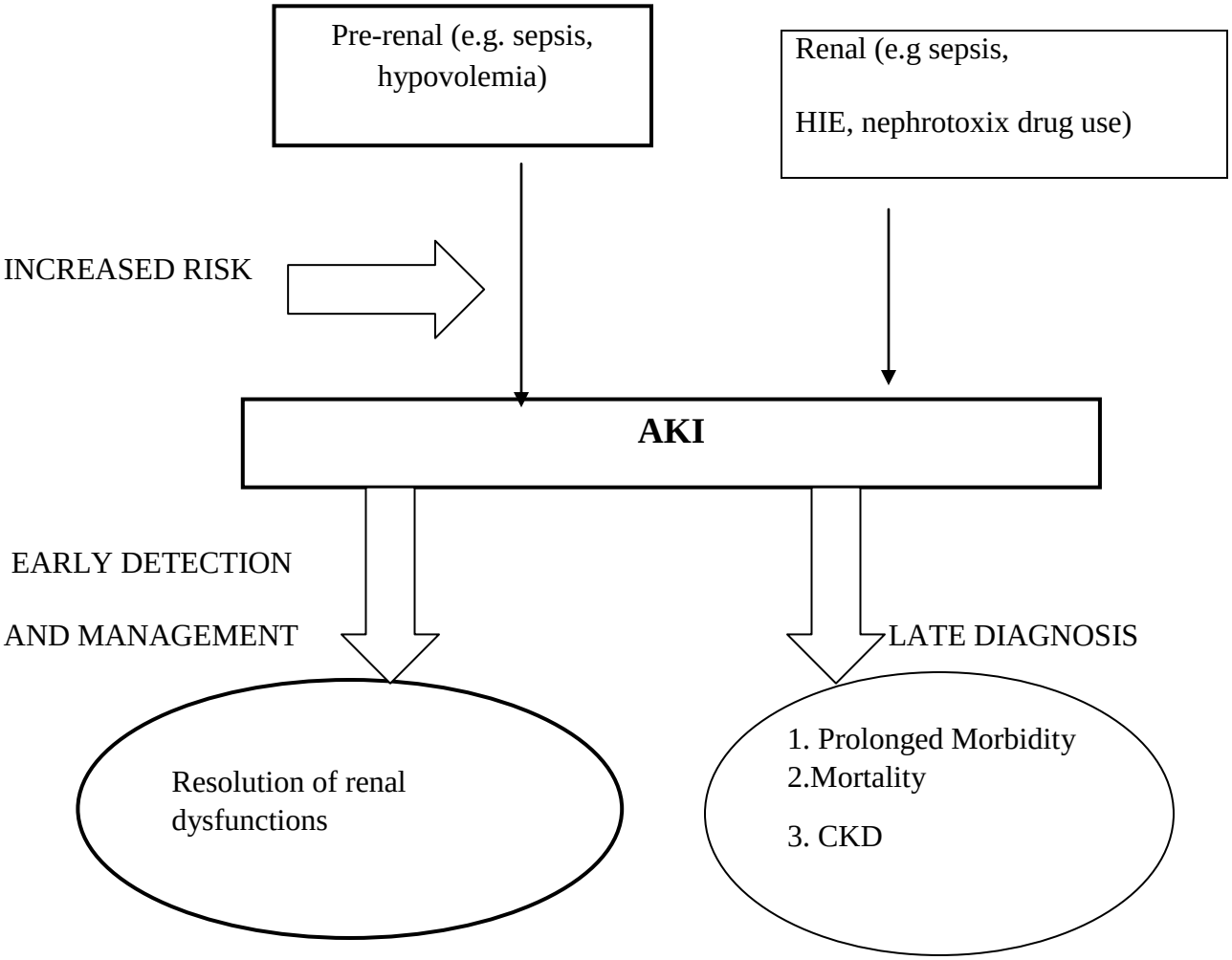


Figure 1: Conceptual framework

1.4 Research Questions

1. What is the prevalence of acute kidney injury among critically ill neonates admitted at MNH?
2. What are the factors associated with acute kidney injury among critically ill neonates admitted at MNH
3. What are the immediate 14 day outcomes of the critically ill neonates with acute kidney injury at MNH?

1.5 Objectives

1.5.1 Broad objective

To determine the magnitude of acute kidney injury and its outcome among critically ill neonates admitted at the Muhimbili National Hospital, in Dar es Salaam.

1.5.2 Specific objectives

1. To determine the prevalence of acute kidney injury among critically ill neonates admitted at Muhimbili National Hospital
2. To determine the factors associated with acute kidney injury among critically ill neonates admitted at Muhimbili National Hospital.
3. To determine the immediate 14-day outcome of critically ill neonates with acute kidney injury admitted at Muhimbili National Hospital.

2.0 LITERATURE REVIEW

2.1 Neonatal renal transition

The human kidney begins to develop from the 5th gestational week. Nephrogenesis is complete at around the 34-36th week of gestation with the formation of millions of nephrons. However, the maturation of the kidney continues through the postnatal period. After birth, there is a rapid increase in glomerular filtration rate and the renal blood flow increases as a result of decreased renal vascular resistance and increase in systemic pressure. To maintain the normal function of the kidney this transition should take place. Failure of this transition can lead to diminished renal function. Renal functions continue to develop from early fetal life up to one year of age. (15)

As nephrogenesis is still ongoing until the gestational age of 34-36 weeks, preterm babies are more at risk of AKI due to a diminished number of nephrons at birth. This means that their transition to normal renal functions is delayed and hence there's prolonged adaptation to extrauterine life due to the immaturity of the kidneys. (16–18) Even in term babies, neonatal kidneys are vulnerable to hypo-perfusion due to their physiology characteristics. Therefore both term and preterm neonates are prone to AKI when critically ill due to their renal physiological adaptation process.

2.2 Neonatal renal functions

Renal functions in the neonate are evaluated through measurements of SCr and urine output (UO). Urine production begins as early as the 9th week of gestational age and continues to increase reaching 25-40ml/hr at term and becomes the major constituent of the amniotic fluid. UO is a predictor of mortality in critically ill neonates. Creatinine is a metabolic product converted from creatine phosphate which is a skeletal muscle by-product. It is freely filtered in the Bowman's space, and its clearance provides a good estimate of GFR. In critically ill neonates, the kidneys have limited adaptive properties in response to stress such as hypoxia, hypovolemia and hence an increment in SCr is expected and is used to monitor the glomerular filtration rate (GFR), which helps in diagnosing and assessing the severity of AKI. (15)

2.3 Prevalence Acute kidney injury in neonates

The prevalence of AKI in neonates is variable and has been found to be 8-24%. (19,20). The variability is brought about by the methods used to diagnose AKI. Several studies had used serum creatinine above 133micromol/l as AKI and hence might have missed some of the neonates with AKI. However, with recent advances in the definitions of AKI, neonates with AKI can be captured early.

In a prospective cohort study done by Halder *et al* in Bangladesh, among 300 sick neonates found the prevalence of AKI to be 4.66% (21) while in Bosnia and Herzegovina, Zulic *et al* looked at acute renal failure in newborns hospitalized in ICU and found a prevalence of 6.84%. (22)

In another study by Bolat *et al* conducted in Turkey found a prevalence of 8.4% among 1992 hospitalized neonates. (23) While in a prospective cohort study by Youssef *et al* which was done in Egypt found that the prevalence of AKI to be 10.8% among 250 neonates admitted in NICU. (24) Similarly, Esfandior *et al* found the prevalence of AKI to be 27.65% among 258 neonates admitted in NICU during the study period. (25) In a multinational observational cohort study looking for incidence and outcome of neonatal AKI (AWAKEN) by Jetton *et al* the prevalence of AKI was reported to be 30%. (10)

There is also variable sexual dimorphism to the prevalence of AKI. Studies show that males and females respond differently to stress and that females are more resilient than males. (26) Some studies show the prevalence to be more in males (24,27) while others had shown females to be more prone to AKI (22,28)

2.4 Factors associated with AKI

The factors leading to AKI in the neonate are many. These factors can be grouped into prerenal, intrinsic and postrenal. Many studies have highlighted similar disease spectrum in these neonates and have been found the commonest to be sepsis, nephrotoxic medications, prematurity, hypoxic-ischemic encephalopathy and many more.

2.4.1 HIE

Asphyxia affects multiple organs causing hypoxia and ischemia. One of the organs commonly affected is the kidney. Kidneys have ability to autoregulation in unstable hemodynamic situation such as ischemia. However, when this autoregulation is disturbed or fails, vasoconstriction and thereafter a reduction of glomerular filtration rate ensues. Neonates who succumb to hypoxia either during antenatal or perinatal period have been found to be at greater risk of developing AKI. Studies have shown different prevalence for AKI associated with HIE. A prospective cohort study done by Alaro *et al* among 60 asphyxiated neonates, in Kenya found the occurrence of AKI in those with HIE to be 11.7% and there was a significant 15folds increase with worsening HIE. (29) While Seleweski *et al* reported it to be 38% among 96 asphyxiated neonates undergoing therapeutic hypothermia. (30)

Similarly in a prospective observational hospital-based study done by Medani *et al* among 85 asphyxiated neonates admitted in tertiary hospital in Sudan found the occurrence to be 54.1% (31) while Shirikhande *et al* in their study on renal functions among 152 asphyxiated neonates in India reported it to be 64%. (32)

2.4.2 Prematurity

Premature kidneys are still developing and when faced with hypoxia or infections are at greater risk of developing AKI. Several studies show that full term and preterm have variable prevalence to AKI and that with decreasing gestational age there is more risk for developing AKI. Some report that term neonates were more prone to AKI (21,27) while others report preterm to be more affected. (24)

In a retrospective study by Stojanovic *et al* reported that 26% of the 150 preterms admitted in neonatal intensive care had AKI. (33) While in another retrospective study by Carmody *et al* in VLBW, the prevalence of AKI was higher 39.8%. (34)

However, in Taiwan, a retrospective study by Daga *et al* that looked at diagnosis and risk factors for AKI in VLBW and reported a lower occurrence of 20.1% based on AKIN criteria and 22.6% based on pRIFLE criteria. (35) Similarly, Lee *et al* did a retrospective cohort study among extremely low birth weight neonates and reported 56% of the 276 developed AKI. (36)

2.4.3 Sepsis

The neonate's immune system is still developing, has a suboptimal immune response and is vulnerable to infection. Infections in the neonate are common, are acquired through hematogenous or transplacental routes and can lead to significant morbidity and mortality.

Neonates are at risk of getting sepsis which can lead to cellular and organ injury if not well treated. Sepsis causes changes in the endothelial tissues functions and can lead to activation of coagulation processes. Over time the exuberant production of pro-inflammatory molecules lead to autoinflammatory immunosuppressive states. Sepsis can cause direct toxicity to tubular cells of the kidney. (37) Mortality in these neonates has also been reported to be high.

In India, an observational hospital-based prospective study was done by Jagrawal *et al* among 107 neonates with septicemia, reported an occurrence of AKI of 21.49% (38) while Marthur *et al* reported the occurrence of AKI to be 26.0% among neonates with sepsis. (13)

In a retrospective study by Vachvanichsanong *et al* among 139 neonates admitted to a tertiary hospital in Thailand sepsis-associated AKI occurred by 30.9%. (39) Higher proportions of 71%-75.6% were reported by Halder *et a*l in Bangladesh, Zulic *et al* in Bosnia, Momtaz *et al* in Iran and El Badawy *et al* in Egypt. (21,22,28,40)

2.4.5 Drug-induced nephrotoxicity

Medications pose a modifiable risk factor. Medication can cause inflammatory changes and they exert different toxic effects on the kidney. Antibiotics use can impair renal functions due to their nephrotoxicity and interactions with renal development particularly in this age group. Among the antibiotics, 80% of AKI are attributed to aminoglycosides such as gentamycin, which is the first line treatment in neonatal infections, whilst 20% is attributed to the use of cephalosporin. (41,42) Aminoglycosides cause tubular cell toxicity by impairing the mitochondrial functions and hence interferes with tubular transport.

El Badawy *et al* in their study on incidence and risk factors of acute kidney injury among critically ill neonates in Egypt found nephrotoxic medication to be associated with 75.6% of AKI. (40)

NSAIDs have also been found to cause changes in intraglomerular hemodynamics. In a study done by Vachanichsanong *et al* proportion of AKI in neonates using indomethacin was found to be 24.4%. (39)

2.4.6 Other factors

Among other factors that are associated with AKI in the critically ill neonates, respiratory distress syndrome (RDS) had a proportion ranging from 34% to 60%. (22,24,25,28) while congenital heart disease (CHD) had a proportion of 7.4% (24) to 8.1% (28) and was attributed by PDA. Surgery also showed to predispose the neonate to AKI, however, multiple factors were involved including hypovolemia, hypotension, and the effect of anesthetic drugs or improper management. This indicated that neonates who undergo surgery should be given closer attention. The Post –surgery prevalence was found to be 11.1% (24)

2.5 Outcome of neonatal acute kidney injury

2.5.1 Resolution of kidney functions

The outcome of neonatal AKI in critically ill neonates is variable. Some of the neonates will have normalization of their renal function with complete recovery and will be discharged from the hospital within the duration of renal function normalization of 7.7 +/- 6.3 days. (28) However, others will have a prolonged hospital stay if not managed on time and will result in progressive uremia, metabolic acidosis, electrolyte imbalance, and fluid overload particularly when the fluid balance is not carefully monitored. Such neonates also require an extended period of follow up at least 90 days to ensure restoration of their kidney functions after treatment of their primary underlying condition. (2,37)

2.5.2 Morbidity and mortality

Studies have also shown that AKI in the newborn period is not only associated with prolonged hospital stay but it has been reported to be associated with an increased neonatal mortality and morbidity. (14,37) A study done by Hossein *et al* in 2011, amongst neonates with AKI in Iran showed that the mortality rate secondary to AKI was 36.7% and sepsis was the leading cause of mortality 30.5%. (28) While other studies reported a higher mortality rate of 50- 65%. (39,40)

3.0 METHODOLOGY

3.1 Study design

This was a cross-sectional study.

3.2 Study setting

The study was conducted at the Muhimbili National Hospital neonatal unit, which is based in Ilala district, Dar es Salaam, Tanzania. Muhimbili hospital is the national referral hospital receiving patients from the 5 municipalities in Dar es Salaam (Ilala, Kinondoni. Kigamboni, Ubungo and Temeke) but MNH also receives referral patients from the other 26 regions of the country. The neonatal ward has a capacity of 140 beds, admitting approximately 20-30 babies per day with an annual admission rate of 6000-8000 neonates. MNH neonatal unit was therefore selected purposively because the majority of critically ill neonates are most likely to be referred for specialist management.

3.3 Study population

All critically ill neonates admitted at MNH neonatal unit were eligible for this study.

3.4 Sample size

The sample size was calculated using the known prevalence of AKI in neonates found in previous studies**.** In a study done in 2013, in Zimbabwe, the prevalence of AKI in neonates admitted in a referral hospital was found to be 33.3%. (4) The sample size was therefore estimated from the formula

$$n = \frac{z^2 p(100-p)}{\varepsilon^2}$$

Where

z= level of confidence (1.96 for 95% confidence level)

p = expected proportion= 0.33

ε = margin of error = 5%

n= 341neonates

An additional 10% non-response rate was added and hence minimum sample was 378 participants.

3.5 Sampling procedure

Critically ill neonates admitted in the neonatal unit were recruited consecutively until sample size was reached. Prior to recruitment, written consent was sought from the parents/caretakers.

3.6 Inclusion criteria

3.6.1. Neonates who were included in the study met the following criteria:

3.6.2. Neonates whose mothers gave consent to participate in the study.

Critically ill neonates presenting with convulsions, inability to feed, vomiting everything, respiratory distress, jaundice, hyper/hypothermia, lethargy, dehydration or shock and those with decreased urine output.

3.7 Exclusion criteria

Neonates who were excluded from the study were:

3.7.1. Neonates who had obvious congenital anomalies of the kidney and urinary tract such as bladder exstrophy, urethral atresia, and polycystic kidney disease, are more likely to have CKD and hence may lead to an overestimation of the findings.

3.8 Data collection

Neonates who were included in the study were assigned a study identification number. A standardized structured English questionnaire was used to collect data. Demographic information including gestational age, birth weight, Apgar score, was obtained from interviewing the mother and by reviewing participants' case notes.

The clinical presentation of the neonate was obtained through physical examination and review of patient case notes. The treatment received by the neonate was also assessed to determine if considerations were made regarding renal safety and this was documented. Neonates were followed for 72 hours to determine the progression of their AKI and at 14 days to document their outcome including discharge from the hospital, prolonged hospitalization or death.

Blood specimen was drawn from recruited participants at admission, after 72hours and at the 14^{th} day. The specimen was drawn from antecubital fossa using aseptic technique, 1ml of venous blood drawn was stored in red-capped vacutainer and transported to the MNH Central Pathology Laboratory. The specimen was analyzed for serum creatinine using Architect plus Ci4100 analyzer. Other tests that were analyzed were blood urea nitrogen (BUN) full blood picture (FBP), C- reactive protein (CRP) and serum electrolytes.

All neonates who developed AKI, had an ultrasound of the kidney, ureter and bladder (KUB) to further define their kidney pathology. The pertinent findings was extracted from the radiological report and documented in the questionnaire.

3.9 Data management and analysis

All questionnaires were checked for consistency. Data entry, cleaning, and analysis was done using statistical package for social science SPSS version 20.0. Continuous variables such as gestational age, birth weight, length, head circumference, were expressed using measures of central tendency. Categorical data such as serum creatinine values were expressed as frequencies or proportions. Univariate analysis was done using chi-square to determine the association between the different associated factors and AKI. Multivariate logistic regression was then used to determine the association between AKI and known associated factors found to be significant on univariate analysis. A p value of less than 0.05 was considered statistically significant.

3.10 Pre-testing of the study tool

Pre-testing of the questionnaire was carried out on 10 neonates whose mothers had consented to ensure that it captured the key variable required to meet the study objectives. This helped to highlight the strengths and expose the weaknesses of the questionnaire prior to beginning the study. Data from the pre- test were not included in the final data analysis.

3.11 Ethical Consideration

Ethical clearance to conduct this study was sought from the MUHAS Research and Ethical Review Committee and permission were obtained from the MNH administration respectively.

Mothers of neonates included in the study were requested to sign a written informed consent form prior to recruitment. This was done after they had received information regarding the importance of this study, its benefits and risks of participating in this study. They were also informed of the procedures that were involved in determining the presence of acute kidney injury which included the taking of blood samples and where necessary an abdominal ultrasound scan. Clinical information obtained in this study was communicated to the physicians taking care of the study participants so that they could be used for their continued clinical care.

All neonates with AKI were followed up to ensure resolution either within their admission in the ward or post discharge in the postnatal clinic at 14 days and 28 days respectively. Furthermore mothers were counseled to look for symptomatology that will show renal dysfunction in the future, which may necessitate linkage to pediatric nephrology clinic.

Confidentiality of participant's information was ensured and no identification was used on the data collection tools except for the laboratory requisition form. Specific study identification numbers were used on the questionnaires such that no information could be traced back to the participants. Information obtained was stored in a password secured computer base and the hard copies of the questionnaire were also secured in a locked cabinet.

4.0 RESULTS

4.1 Social-demographic characteristics of the study participants

A total of 378 neonates were enrolled in this study. Majority of these neonates were age ≤ 7 days 306 (81%) with predominantly male 226(59.8%). Most 281(74.3%) had birth weight above 2500 grams and an Apgar score above 7 (82.5%). Majority 295(78%) were full term infants. The median age (Inter-Quartile Range) at admission was 3 (1, 6) days.

Table 1: Socio-Demographic characteristics of study participants (n=378)

Demography	N (%)
Age (Days)	
≤ 7	306 (81.0)
8 to 14	43 (11.4)
15 to 28	29 (7.7)
Sex	
Male	226 (59.8)
Female	152 (40.2)
Birth weight (g)	
Normal (2500 and above)	281 (74.3)
Low birth weight (1500-2499)	70 (18.5)
Very low birth weight (1000-1499)	24 (6.3)
Extremely low birth weight (<1000)	3 (0.8)
Apgar score at 5th minute	
≤ 6	66 (17.5)
≥7	312 (82.5)
Gestational age	
≥37 weeks	295 (78.0)
<37 weeks	83 (22.0)

4.2 Prevalence of AKI among critically ill neonates

A total of 119 (31.5%) had AKI as shown in figure 2. Majority had stage 1 AKI (78.2) % while stage 2 was 9.2% and stage 3 was 12.6% as per nKDIGO classification.

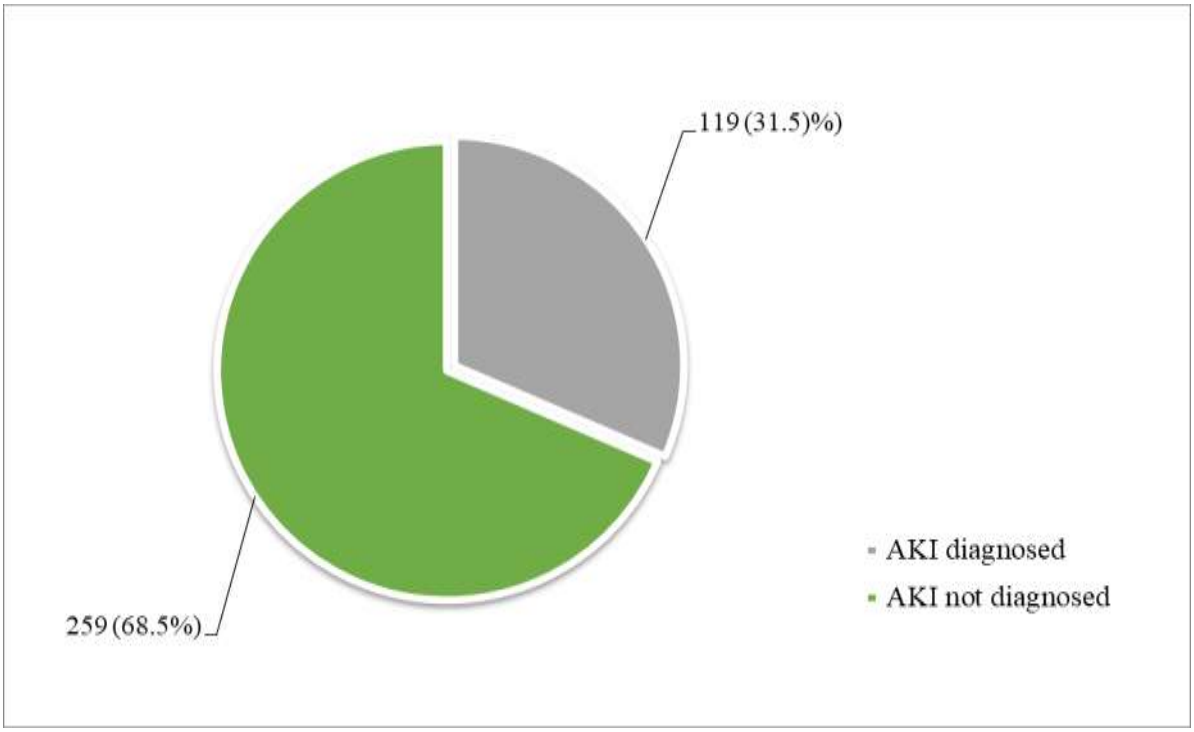


Figure 2: Pie chart showing proportion of Acute Kidney Injury (AKI) among studied critically ill neonates admitted at MNH (n=378)

4.3 Trend of serum creatinine

The scatter diagram below showing the 378 neonate's serum creatinine at baseline and their follow up. The median SCr was 166.5 µmol/L with maximum SCr of 1338 µmol/L.

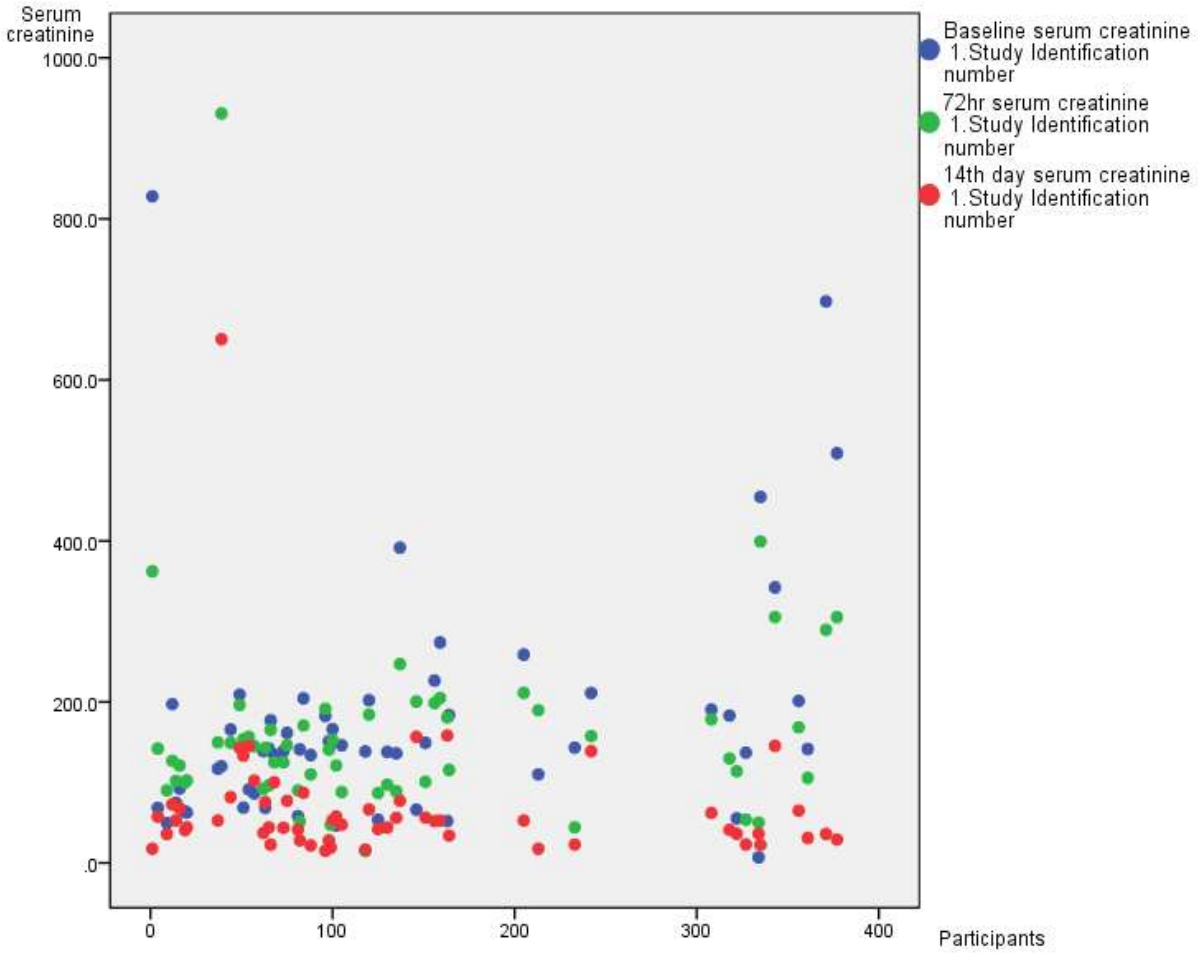


Figure 3: Trend of SCr at baseline and follow up of the 378 studied participants

4.4 Factors associated with AKI

Factors that were significantly associated with AKI were neonatal sepsis (p=0.004), intestinal obstruction (0.021), severe pneumonia (p=0.001), meningitis (p=0.049) and gentamycin use (p=0.014) as shown in table 2.

Table 2: Factors associated with AKI (n=378)

Variable	With AKI N (%)	Without AKI N(%)	*p*- value
Age(Days)			
≤ 7	92 (30.1)	214 (69.9)	
8 to 14	18 (41.9)	25 (58.1)	
15 to 28	9 (31.0)	20 (69.0)	**0.296**
Sex			
Male	69 (30.5)	157 (69.5)	
Female	50 (32.9)	102 (67.1)	**0.628**
Gestational age			
≥37 weeks	90 (30.5)	205 (69.5)	
<37 weeks	29 (34.9)	54 (65.1)	**0.443**
Neonatal sepsis			
Yes	32 (22.4)	111 (77.6)	
No	87 (36.9)	149 (63.1)	**0.004**
Intestinal obstruction			
Yes	18 (60.0)	12 (40.0)	
No	101 (29.0)	247 (71.0)	**0.021**
Severe pneumonia			
Yes	4 (16.7)	20 (83.3)	
No	115(32.5)	239 (67.5)	**0.001***
Congenital Heart Disease			
Yes	3 (75.0)	1 (25.0)	
No	116(31.0)	238 (69.0)	**0.102***
Prematurity with RDS			
Yes	19 (32.8)	39 (67.2)	
No	100 (31.3)	220 (68.8)	**0.820**
Meningitis			
Yes	6 (60.0)	4 (40.0)	
No	113 (30.7)	255 (69.3)	**0.049***
HIE			
Yes	37 (33.9)	72 (66.1)	
No	82 (30.5	187 (69.5)	**0.512**
Gentamycin used			
Yes	113 (30.5)	257 (69.5)	
No	6 (4.7)	121 (95.3)	**0.014**

Intestinal obstruction included those with hypertrophic pyloric stenosis, duodenal atresia, anal atresia and trachea esophageal fistula**. *Fischer exact test was used**

4.5 Multivariate logistic regression

The following factors were noted to be independent predictors of AKI, neonatal sepsis (aOR 2.237, 95%CI 1.3-3.6, P=0.001), severe pneumonia (aOR3.0, 95%CI 1.0-9.3, P=0.047) and usage of gentamycin (aOR6.8, 95%CI 1.3-9.3, P=0.02) as shown on table 3.

Table 3: Logistic regression on risk factors for AKI (n=378)

Risk factor	**Crude OR (95% CI)**	***p-value***	**Adjusted OR (95% CI)**	***p-value***
Neonatal sepsis				
Yes	2.007 (1.249-3.225)		2.237 (1.375-3.637)	
No	1	0.004	1	0.001
Intestinal Obstruction				
Yes	2.793 (1.171-6.661)		0.492 (0.200-1.211)	
No	1	0.001	1	0.123
Meningitis				
Yes	3.385 (0.937 – 12.228)		0.4002 (0.106-1.517)	
No	1	0.049	1	0.178
Severe Pneumonia				
Yes	3.668 (1.705 -7.893)		3.083 (1.017-9.399)	
No	1	0.106	1	0.047
Congenital heart disease				
Yes	6.672 (0.687-8.428)		0.199 (0.020-1.951)	
No	1	0.060	1	0.166
Gentamycin used				
Yes	6.823 (1.356-8.423)		6.830 (1.321-9.399)	
No	1	0.007	1	0.022

4.6 Ultrasound findings of participants with AKI

Seventy four (70.5%) participants with AKI had normal kidney ureter and bladder ultrasound (KUB), twenty five (23.8%) had increased echogenicity, four (3.81%) had mild hydronephrosis and two (1.9%) had ectopic kidney. Fourteen participants with AKI did not have an ultrasound KUB since they died before 48hours.

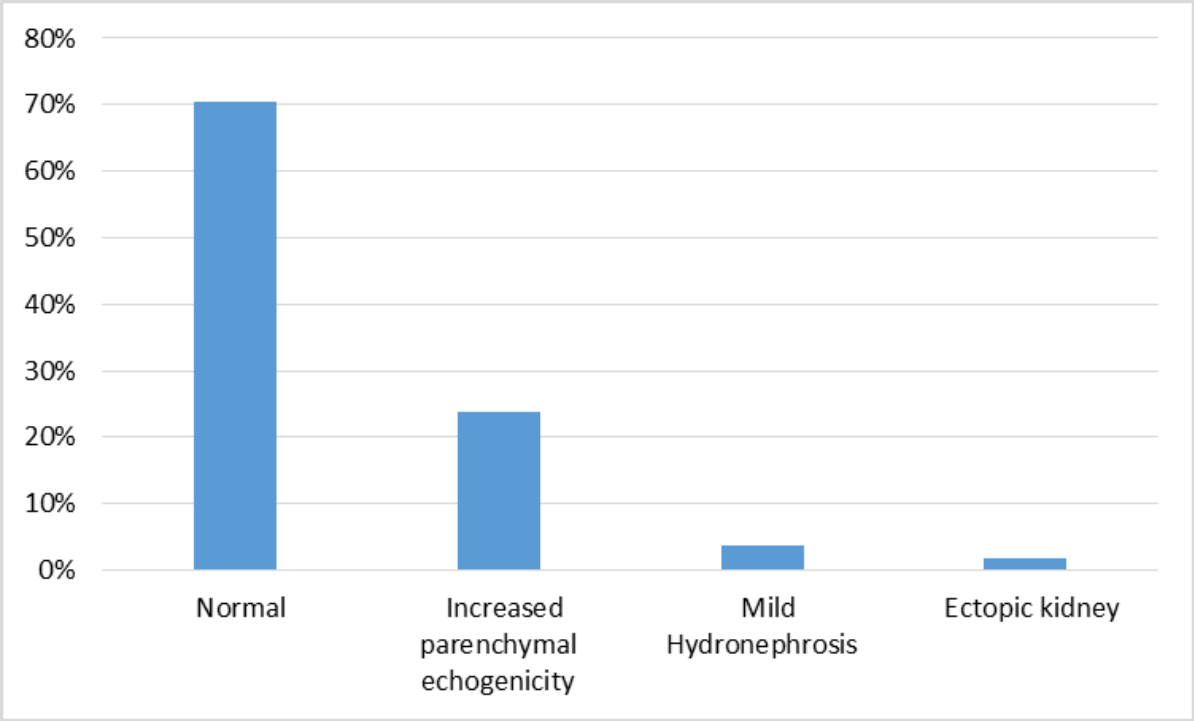


Figure 4: Distribution of findings on KUB ultrasound (n=105)

4.7 Outcome for patients with AKI

Overall mortality in this study was 22.5% (85), participants with AKI had significantly higher mortality (70.6%) as compared to those without AKI (29.4%) p value of 0.000. Among those with AKI, 62.5% had longer hospital stay of more than fourteen days compared to 37.5% without AKI and p value of 0.006.

Table 4: Outcome for patients with AKI (n=119)

Outcome	With AKI	Without AKI	*p*- value
Mortality			
Dead	60 (70.6)	25 (29.4)	
Alive	59 (20.1)	234 (79.9)	**0.000**
Hospital stay			
≥14	10 (62.5)	6 (37.5)	
<14	109 (30.1)	253 (69.9)	**0.006**

4.8 Resolution of renal functions

A total of 59 participants with AKI survived and among them most had a resolution of serum creatinine by fourteenth day (83.0%) with average time of resolution 4.5 ± 8.3 days while 16.9% had resolution of renal dysfunction beyond the fourteenth day.

Table 5: Resolution of renal function among those with AKI (n=59)

Resolution of AKI	N (%)
72 hours	19 (32.2)
14 days	30 (50.8)
28 days	10 (16.9)

5.0 DISCUSSION

5.1 Prevalence

This study was carried out among 378 critically ill neonates admitted at MNH neonatal unit from October, 2017 to March, 2018. The aim of this study was to determine the burden of AKI, its associated factors and outcome. One hundred and nineteen participants (31.5%) were noted to have AKI. This finding is remarkably high showing the significant burden of this condition in our setting.

The prevalence noted in this study is comparable to the 33.3% reported by Matyanga *et al* in a study conducted among neonates admitted in a tertiary hospital in Zimbabwe. (4) Findings from this study and one by Matyanga *et al* indicate that AKI is common among neonates in the region.

In contrast to our findings, Momtaz *et al* and Gharehbaghi *et al* reported lower prevalence of AKI of 1.54% and 2.83% respectively. (14,28) Similarly, Halder *et al* in Bangladesh (21) and Youssef *et al* in Egypt (24) reported the occurrence of AKI to be 4.6% and 10.8% respectively. The differences could be attributed to differences in definitions of AKI used in these studies as well as the setting for neonatal care. These studies used a cut off of serum creatinine of 133µmol/l as their definitions for AKI whereas this study used nKDIGO definitions which enabled to diagnose neonates with AKI in their earliest stages. The findings of AKI prevalence in this study highlights the importance of clinicians to have a high index of suspicion for AKI for all critically ill neonates admitted in the neonatal unit.

5.2 Factors associated with acute kidney injury

In this study, the majority of the patients were admitted due to sepsis and it was found to be an independent predictor of AKI. This is in keeping with most reported epidemiological studies done by Halder *et al* in Bangladesh, Youssef *et al* in Egypt and Momtaz *et al* in Iran. (21,24,28) In Thailand, a retrospective study done by Vachvanichsanong *et al* reported sepsis-associated AKI to be 30.9%. (39) Whereas, in Iran Gharehgabhi *et al*, Ghobrial *et al* and Momtaz *et al* reported that sepsis was the most predisposing factor for AKI occurring at

32.9% to 77.5% respectively. (14,28,43) Youssef *et al* prospectively followed 250 neonates admitted in NICU, in Egypt, and reported the most common factor associated with AKI was sepsis occurring at 63%. (24) Therefore it is evident that surveillance of renal functions is warranted in neonates admitted with sepsis.

The association between nephrotoxic drugs and AKI has been reported in several studies and it poses a modifiable risk factor. In this study, majority of the participants with exception of eight of them had received gentamycin as first-line therapy. Among them, 30.5% developed AKI. This shows that clinicians need a robust appreciation of the potential contributory effects of gentamycin to AKI in critically ill neonates. These findings are in consistency with studies done by EL Badaway *et al* in Cairo and Gharehbaghi *et al* in Iran that reported an occurrence of 75.6% and 43.5% respectively of AKI to be attributed to nephrotoxic medication. (14,40)

The crosstalk between kidney and lung via cytokines and inflammation has been demonstrated. (36) Severe pneumonia causes peritubular hypoxia and hence leads to AKI. This study demonstrated that one- quarter of those with severe pneumonia developed AKI. Similarly, this study found that 60% of those who had meningitis developed AKI. AKI in meningitis results from hypotension, hypoxemia, and hypoperfusion which leads to cortical necrosis.(44) This calls for utmost attention to be given to those neonates who present with meningitis in order to diagnose them early and offer proper management.

In this study, intestinal obstruction such as hypertrophic pyloric stenosis, duodenal atresia, tracheoesophageal atresia and anal atresia was found to be associated with AKI. Twelve had developed AKI at admission while six developed AKI after surgery. The surgery itself does not cause AKI however, one could postulate that the factors such hypovolemia, dehydration anesthetic medications might have led to AKI. (24) Gharehbaghi *et al* found the occurrence of AKI in those who underwent surgery to be 43.5%. (14) Similarly, Mortazavi *et al* (27) reported that 37.7% of their patient had developed AKI following surgery while Youssef *et al* reported it to be 11.1% and the main reason for surgery was gastrointestinal anomalies. (24) Clinicians should be vigilant to any patient presenting with intestinal obstruction and in those who undergo surgery in order to detect early and ameliorate the progression of AKI.

Kidney, ureter and bladder ultrasound performed for participants with AKI revealed normal, increased parenchymal echogenicity, mild hydronephrosis and ectopic kidney. These findings are in line with reports from other similar studies. In a study done by Momtaz *et al* in Iran, ultrasound KUB revealed normal, hydronephrosis and nephrocalcinosis. (28) In contrast, Vachvaningsanong *et al* reported nine of the neonates with AKI had obstructive uropathy such as posterior urethral valve, ureteropelvic junction, and cystic lesion in the bladder, exstrophy bladder anorectal malformation while three had non-obstructive findings such as cystic kidney disease. (39)

5.3 Outcome

Neonatal mortality is a global challenge, and sub-Saharan African countries are affected. In this study, the overall mortality was 22.5% which is very high and was significantly higher among those neonates with AKI 70.6% as compared to those without AKI 29.4%. The findings of this study show that AKI is an important factor in mortality attributed to neonatal sepsis, prematurity and birth asphyxia which are the leading cause of neonatal mortality globally.

In contrast, lower mortality rates were reported in upper-middle-income countries such as Turkey, Thailand and Iran. In Turkey, the mortality rate reported was 23.6% (23) while in Iran, the mortality rates ranged from 4.5% to 36.7%. (14,25,28,45) Similarly, in Bosnia, the mortality rate was 36.7% (22) while in Thailand it was 38.8%. (39) The lower mortality rates could be attributed to variation in treatment practice, including well capacitated laboratory services which enable early detection, treatment and preventive strategies.

This study demonstrated that 62.5% neonates had a prolonged hospital stay beyond fourteen days due to persistent renal dysfunctions. This is in keeping with other studies that showed those who had developed AKI had prolonged hospital stay as reported by Zulic *et al* and Momtaz *et al*. (22,28) The persistence in renal dysfunction might as well be brought about by the severity of underlining illness.

Among survivors of AKI, the majority had a resolution of their renal functions by the fourteenth day (83%). Our findings were similar to other studies that reported a resolution of renal functions in 40%-84% and average time taken was more than 7 ± 6 days which was seen in studies done by Zulic *et al* in Bosnia, (22) Mortazavi *et al* (27), Momtaz *et al* in Iran (28)and Kapoor *et al in* Iran. (45) Ten neonates required follow up beyond fourteen days as they had persistent of renal dysfunction however they resolved by 28 days of life.

5.4 Strength

This was the first study that addressed the prevalence, associated factors and early outcome of AKI among critically ill neonates in our setting. In this study, classification of AKI based on nKDIGO criteria including documentation and monitoring was done until resolution of renal dysfunction.

6.0 CONCLUSION AND RECOMMENDATION

6.1 Conclusion

AKI is prevalent among critically ill neonates and has a high mortality rate. The independent predictors of AKI noted were neonatal sepsis, severe pneumonia and usage of gentamycin. Significantly higher mortality was noted in those with AKI as compared to those without AKI.

6.2 Recommendation

6.2.1 Clinicians should actively diagnose, manage and document AKI in all critically ill neonates admitted in the hospital.

6.2.2 Neonates with AKI should be followed up for not less than 28 days because although majority had resolution at 14 days, a significant few had prolonged renal dysfunction up to 28 days of life so as to ensure complete cure.

6.2.3 All neonates with documented AKI should be entered into a database which can be linked to the MNH nephrology unit should they develop future renal dysfunctions.

REFERENCES

1. Kliegman R, Stanton B, St. Geme JW, Schor, N. F. &, Behrman RE. Nelsons textbook, 20th edition. In: Nelsons Textbook. 2016. p. 789–94.

2. Willis K, Cheung M, Slifer S. Clinical Practice Guideline for Acute Kidney Injury KDIGO. Int Soc Nephrol. 2012;2(1):13–23.

3. Hasari BYA, Zübarioğlu AU, Bülbül A, Uslu HS. Neonatal Acute Kidney Injury. J Acad Res Med. 2013;3:53–9.

4. Matyanga P, Kandawasvika G, Muchemwa L, Mujuru H. Prevalence of Acute Kidney Injury in neonates admitted at a referral hospital,Harare,Zimbabwe. Cent Africa J Med. 2013;59(1):1–6.

5. Radhakrishnan J, Kiryluk K. Acute renal failure outcomes in children and adults. Kidney Int. 2006;69(1):17–9.

6. Mammen C, Al Abbas A, Skippen P, Et A. Long-term risk of CKD in children surviving episodes of acute kidney injury in the intensive care unit: a prospective cohort study. American journal of Kidney Disease. 2012;59: 523–30.

7. Greenberg J, Coca S, Parikh C. Long-term risk of chronic kidney disease and mortality in children after acute kidney injury: A systematic review. BMC Nephrology. 2014;15:184.

8. Carmody JB, Charlton JR. Short-Term Gestation, Long-Term Risk: Prematurity and Chronic Kidney Disease. Pediatrics. 2013;131:1168–79.

9. Akcan-Arikan A, Zappitelli M, Loftis L, Washburn K, Jefferson L, Goldstein S. Modified RIFLE criteria in Critically ill children with acute kidney injury. Kidney Int. 2007;71(10):1028–1035

10. Jetton J, Askenazi D, Seleweski D, Charlton J, Guillet R. Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates, Design of a Retrospective Cohort Study. Front Pediatr. 2016;4:68.

11. Patzer L. Nephrotoxicity as a cause of acute kidney injury in children. Pediatr Nephrol. 2008;23(12):2159–73.

12. Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Critical care (London, England). 2013;17: 204.

13. Mathur NB, Agarwal HS, Maria A. Acute renal failure in neonatal sepsis. Indian J Pediatr. 2006;73(6):499–502.

14. Gharehbaghi M, Peirovifar A. Evaluating causes of acute renal failure in newborn infants. Pakistan Journal of Medical Sciences. 2007;23: 877–80.

15. Bitsori M. 2. The development of renal function. Essentials Pediatr Urol. 2012;37/661(2):9–20.

16. Sutherland MR, Gubhaju L, Moore L, Kent AL, Dahlstrom JE, Horne RSC, et al. Accelerated maturation and abnormal morphology in the preterm neonatal kidney. J Am Soc Nephrol. 2011;22:1365–74.

17. Kandasamy Y, Smith R, Wright IMR, Lumbers ER. Extra-uterine renal growth in preterm infants: Oligonephropathy and prematurity. Pediatr Nephrol. 2013;28(9):1791–6.

18. Black MJ, Sutherland MR, Gubhaju L. Effects of Preterm Birth on the Kidney. In: Basic Nephrology and Acute kKdney Injury. 2009: 61–78.

19. Ottonello G, Dessì A, Neroni P, Elisabetta M, Manus D, Fanos V. Acute kidney injury in neonatal age. 2014;3(2):1–7.

20. Torres C, Bezerra DM. Defining reduced urine output in neonatal ICU : Importance for mortality and Acute Kidney Injury classification. Nephrol Dial Transplatation. 2013;28:901–9.

21. Halder S, Sonia S, Biswas S, Hoque M. Acute Kidney Injury in Sick Neonate. J Bangladesh Coll Physicians Surg. 2017;35(1):20–3.

22. Evlijana Z, Devleta H. Acute renal failure in the newborns hospitalized at the intensive care unit , university clinical centre Tuzla. Pediatr Neonatol. 2015;10(1):47–50.

23. Bolat F, Bolat G, Comert S, Can E, Kucuk O. Acute kidney injury in a single neonatal intensive care unit in Turkey. World J Pediatr. 2013;9(4):323–9.

24. Youssef D, Abd-elrahman H, Shebab M, Abd-Erlheem M. Incidence of acute kidney injury in the neonatal intensive care unit. Saudi Nephrol Dial Transplant. 2015;26(1):67–72.

25. Esfandiar N, Mohkam M, Afjeii A. Prognostic factors and mortality rate in neonates with Acute Renal Injury in NICU. Pediatr Nephrol. 2013;1(1):32–6.

26. Lima-Posada I, Portas-Cortés C, Pérez-Villalva R, Fontana F, Rodríguez-Romo R, Prieto R, et al. Gender differences in the acute kidney injury to chronic kidney disease transition. Scientific Reports 2017;7(1):12270

27. Mortazavi F, Sakha SH. Acute kidney failure in neonatal period. Iran J Kidney Dis. 2009;3(3):136–40.

28. Momtaz H, Sabzehei M, Rasuli B, Torabian S. The main etiologies of acute kidney injury in the newborns hospitalized in the neonatal intensive care unit. J ClinNeonatol. 2014;3: 99–102.

29. Alaro D, Musoke R, Lucy M, Bashir A. Prevalence and Outcomes of Acute Kidney Injury in Term Neonates with Perinatal Asphyxia. Afr Health Sci. 2013;14(3):682–8.

30. Seleweski D, Charlton J, Jeton J, Guillet R, Askenazi D. Neonatal Acute Kidney Injury, State of the art. Pediatrics. 2015;136(2):463–73.

31. Medani S, Kheir A, Mohamed M. Acute kidney injury in asphyxiated neonates admitted to a tertiary neonatal unit in Sudan. Sudan J Pediatr. 2014;14(2):29–34.

32. Shrikhande DY, Singh V, Garg A. Study of renal functions in neonatal asphyxia. Pravara Med Rev. 2016;8(4):12–7.

33. Stojanović V, Barišić N, Milanović B, Doronjski A. Acute kidney injury in preterm infants admitted to a neonatal intensive care unit. Pediatr Nephrol 2014;(May):2213–20.

34. Carmody J, Swanson J, Rhone E, Charlton J. Recognition and Reporting of AKI in Very Low Birth Weight Infants. Clin J Am Soc Nephrol. 2014;9(12):2036–43.

35. Daga A, Dapaah-Siakwan F, Rajbhandari S, Arevalo C, Salvador A. Diagnosis and risk factors of acute kidney injury in very low birth weight infants. Pediatr Nephrol. 2017;58(3):258–63.

36. Lee C, Chan O, Lai M, Lim W. Incidence and outcomes of acute kidney injury in extremely-low-birth-weight infants. PLoS One. 2017;12(11):187764.

37. Selewski DT, Charlton JR, Jetton JG, Guillet R. Neonatal Acute Kidney Injury. Am Acad Pediatr. 2015;136(2):463–73.

38. Rajappa SA, Shaji J. A Clinical Study of Suppurative Keratitis. Int J Biomed Res. 2015;6(11):869–73.

39. Vachvanichsanong P, McNeil E, Dissaneevate S, Dissaneevate P, Chanvitan P, Janjindamai W. Neonatal acute kidney injury in a tertiary center in a developing country. Nephrol Dial Transplatation. 2015;27(3):973–7.

40. El Badaway A, Makar S, Abdel-Razak A, Elaziz A. Incidence and risk factors of acute kidney injury among the critically ill neonates. Saudi J Kidney Dis Transplant. 2015;26(3):549–55.

41. Fanos V, Cataldi L. Renal transport of antibiotics and nephrotoxicity: a Review. J Chemother. 2001 Jan 1;13(5):461–72.

42. Blatt E, Scott E, D LM. Drug induced acute kidney injury. Hospital Medicine Clinics. 2013;2: 1–17.

43. Ghobrial E, Elhouchi S, Eltatawy S, Beshara L. Risk factors associated with acute kidney injury in newborns. Saudi J Kidney Dis Transplant. 2018;29(1):81–7.

44. Kennedy C, Khilji S, Dorman A, Walshe J. Bilateral renal cortical necrosis in meningococcal meningitis,case report. 2011;2011.:3.

45. Kapoor K. Predictors of Mortality in Out Born Neonates with Acute Renal Failure; an Experience of a Single Center. Iran J Pediatr. 2013;23(3):321–6.

APPENDICES

Appendix I: Questionnaire

DEMOGRAPHIC INFORMATION

A. Participant's information

1. Study identification number _____
2. Date of birth _____
3. Date of admission _____
4. Place of birth _____
5. Gender 1. Male 2. Female
6. Age _____days
7. GA in weeks _____
8. Apgar score 1st minute_____ Apgar 5th minute_____
9. Birth weight _____grams
10. Length _____ cm
11. OFC _____cm

B, Mother's information

12. Age _____years
13. Parity 1. Prim gravida 2. multigravida
14. Mother's serology status HIV_____ VDRL_____
15. Maternal illness 1.pre-eclampsia 2.pre-partum hemorrhage 3.others_____ 4.none

C. History of the patient

D. Presenting symptoms

19.Fever	1.Yes 2.No T_____	.abdominal distension	1.yes 2.No
20.Convulsions	1.Yes	6.jaundice	1.yes

	2.No		2.No
3.Poor feeding	1.Yes 2.No	7.decreased urine output	1.Yes 2.No
4.difficulty in breathing	1.Yes 2.No RR_____	8.Bleeding	1.Yes 2.No
Vomiting		9.Others	

E. Diagnosis(es)_____

F. Antibiotic used since onset of illness 1.Gentamycine 2.Ampiclox 3.Ceftriaxone

G. Laboratory

1.Scr micromol/l	1.baseline_____ 2.above normal for age_____
2.BUN milimol/l(mmol/l)	
3.WBC k/ul	
4.absolute neutrophil count	
5.Hemoglobin g/dl	
65.Platelets k/ul	
7.CRP	
8.K	
9.Na	

10.Chloride	
11.magnesium	
12.phosphorus	
13.calcium	
14.blood culture	

H. Medications adjusted: 1. Yes 2. No

I. KUB findings

1. PUV 2. UPJ 3.VUR 4. Increased parenchymal echogenicity 5.Normal 6.Others_____

J. Follow up

72hours	14^{th} day	28^{th} day

K. Outcome

1. Recovered	Date
2. Prolonged hospital stay	
3. Death	Date

Appendix II: Consent Form – English

STUDY IDENTIFICATION NO. ----------

TITLE: THE PREVALENCE, ASSOCIATED FACTORS AND EARLY CLINICAL OUTCOMES OF CRITICALLY ILL NEONATES WITH ACUTE KIDNEY INJURYAT MUHIMBILI NATIONAL HOSPITAL, DAR ES SALAAM

I am Dr. Naomi Mwamanenge, MMED Pediatrics and Child Health student. I am conducting a study on the prevalence and risk factors of kidney injury amongst critically ill neonates admitted at Muhimbili National Hospital. This will help in timely management in order to improve quality of care of your critically ill newborn with acute kidney injury.

Participation

You are free to volunteer to participate in the study but you are also free to decline to participate the study. Even if you do wish to participate in this study, your newborn infant will continue to receive the standard treatment.

Confidentiality

Your information will be secured. A study identification number will be given to your newborn infant so that no names or identification will appear on your study records except on the laboratory request form. In so doing, confidentiality will be ensured. Information obtained will only be used for research purpose and will be kept in a password secured computer only accessed by the researcher and the hardcopies of the questionnaires will be stored in a locked cabinet.

Procedure

We will take a 1 milliliter blood sample from your neonate once we diagnose kidney injury and after 72 hours we will take a second 1 milliliter blood sample to check for resolution of normal kidney functions. We shall give you feedback on the results as soon as we receive them from the laboratory. Where indicated, some neonates may have an abdominal ultrasound done to further determine the extent of their kidney damage. The urine output of your newborn

will also be monitored daily by cauterization and collection for those newborns with confirmed acute kidney injury.

Cost

If you consent to participate in this study, you shall not incur any additional costs other than your normal hospital fees.

Payment

You shall not be paid in case you consent to participate in this research.

Benefits

By participating in this study, your newborn infant will benefit from timely recognition of the presence of kidney injury in your newborn infant and early initiation of appropriate management and thereafter follow up.

Risks

There will be drawing of two blood samples from your newborn infant and this will cause mild to moderate short-lived pain at the puncture site. Other risks include mild bleeding and bruising though done correctly may not lead to such complications.

Who to contact

If you have any queries with regard to this study, kindly contact the principle investigator, Dr. Naomi Amon Mwamanenge, 0785-398087. If you have any questions about your rights as a participant in this study, you may contact Dr. Joyce Masalu, Chairperson of the Senate of Research and Publications Committee, MUHAS P.O Box 65001, Dar es Salaam (Tel: 2150302-6)

Consent

I voluntary consent for me and my newborn infant to voluntarily participate in this study after reading the consent form or having the information contained in this consent form read aloud to me.

Mother's name_____ Signature _____ Date _____

Investigator's name _____ signature ___ _____ Date _____

Appendix III: Fomu Ya Ridhaa Kwa Mzazi

Namba ya utambulisho----------

KICHWA CHA HABARI: UTAFITI KUHUSU UKUBWA WATATIZO, VISABABISHI HATARISHI VYA MAGONJWA YA FIGO KWA WATOTO WACHANGA WALIOMAHUTUTI WALIOLAZWA KATIKA WODI YA WATOTO, MUHIMBILI.

Mimi ni Daktari Naomi Mwamanenge, mwanafunzi wa shahada ya uzamili ya udaktari wa watotokatika Chuo cha Sayansi Shirikishi cha Muhimbili. Mtoto wako anaombwa kushiriki katika utafiti huu.

Je dhumuni la utafiti huu ni nini?

Dhumuni la utafiti huu ni kuchunguza ukubwa wa tatizo navisababishi hatarishi vya magonjwa ya figo kwa watoto wachanga wenye umri chini ya siku 28 tangu wazaliwe, waliolazwa katika Hospital kuu ya Taifa, Muhimbili

Utunzaji wa siri

Taarifa utakazotoa kuhusiana na utafiti huu zitatunzwa kwa usiri mkubwa kwenye kompyuta zenye ulinzi na rekodi zilizopo kwenye makaratasi zitafungiwa kwenye kabati. Ni wafanyakazi wanaohusika na utafiti tu ndio watakaoweza kuona taarifa, na taarifa hizi zitatunzwa siku zote.

Utaratibu utakaotumika kufanya utafiti huu

Tutachukua damu kwa mtoto wako mara tutakapo gungua kuathirika kwa figo, na zoezi hili litarudiwa tena baada ya masaa 72 ili kuthibitisha kuwa figo haiendelei kuathirika au la. Pale itakapo hitajika, mtoto anaweza kufanyiwa kipimo cha altrasaundi ili kuchunguza Zaidi madhara yaliyo sababisha uharibifu wa figo. Kiwango cha mkojo kitachunguzwa kila siku kwa mgonjwa aliyethibitika kuwa figo imejeruhiwa.

Je kuna athari gani za kushiriki katika utafiti huu?

Mtoto wako atatolewa damu kutoka mkono moja, atapata maumivu kidogo na kutoka tone kidogo la damu baada ya kutolewa damu ila ni athari kwa mda mfupi usiozidi dakika moja hadi mbili.

Gharama ya huu utafiti

Hakuna gharama ya nyongeza zaidi katika huu utafiti kama utakubali kushiriki.

Kulipwa kwa kushiriki

Kwa kuwa lengo ni kutaka kupata ufumbuzi wa tatizo hili, kushiriki kwako kutakuwa ni mchango mkubwa hiyvo hakutakuwa na malipo yoyote endapo uta shiriki.

Uhuru wa kushiriki

Ni hiari ya mzazi kushiriki kwenye utafiti huu na pia unaweza kujitoa wakati wowote. Vile vile kutoshiriki au kujitoa kwenye utafiti huu ni haki yako wala hakumnyimi mtoto wako haki yake ya kupata huduma za matibabu.

Faida za kukubali kushiriki

Endapo mtoto atagundulika kuwa na shida atapata matibabu kwa wkati na uangalizi wa karibu.

Ni matumainikwamba taarifa za utafiti huu zitasaidia kuboresha tiba kwa watoto wachanga wengine wenye tatizo la figo kwa siku za baadaye

Je utampigia nani kuhusu utafiti huu?

Kama una maswali kuhusu utafiti unaweza kumpigia daktari wako au mwendesha utafiti huu: Dr Naomi Amon Mwamanenge, 0785398087 muda wa masaa ya kazi. Kama una swali kuhusu haki zako kama mshiriki unaweza kuwasiliana na Dr Joyce Masalu, Mkurugenzi wa Kamati ya Kitengo cha Utafiti, Chuo Kikuu Cha Sayansi na Tiba Cha Muhimbili, S.L.P 65001, Dar es Salaam, Namba ya Simu 2150302-6

Ridhaa

Nimesoma/au nimesomewa maelezo katika fomu hii ya ridhaana nimepewa muda wa kuuliza maswali.

Nakubali kushiriki katika utafiti huu kwa hiari yangu bila kushurutishwa na mtu.

Jina la mama _____Sahihi ya mama _____ Tarehe _____

Jina la Mtafiti _____Sahihi ya mtafiti _____ Tarehe _____