

**PREVALENCE, SEVERITY AND CLINICAL CHARACTERISTICS OF ACUTE
KIDNEY INJURY AMONG CHILDREN WITH SEVERE MALARIA AT MULAGO
HOSPITAL**

By

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fulfillment of the requirements for a Master's Degree In Paediatrics And Child Health**

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DECLARATION

I, Akobye Winnie hereby declare that this is my original work that has never been presented to any other educational institution for any award. Any other Authors' work utilized herein is accordingly acknowledged.

Signature

Date

Akobye Winnie

DEDICATION

This book is dedicated to my dearest family.

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I am grateful to the merciful God almighty who has brought me thus far!

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LIST OF ACRONYMS

ACE	Angiotensin converting enzyme
ACU	Acute care unit
AKI	Acute Kidney Injury
ARF	Acute Renal Failure
CBC	Complete blood count
CD	Cluster of differentiation
EDTA	Ethylenediaminetetraacetic acid
ELA	Endothelial leucocyte adhesion molecule
GFR	Glomerular Filtration Rate
ICAM	Intercellular Adhesion Molecule-1
IL	Interleukin
LDH	Lactate Dehydrogenase
PI	Principle Investigator
pRIFLE	Modified Paediatric RIFLE
RIFLE	Risk, Injury, Failure, Loss of kidney function, End stage renal disease
USS	Ultrasound scan
VCAM-1	Vascular Cell Adhesion Molecule-1
WHO	World Health Organization

OPERATIONAL DEFINITIONS

Acute kidney injury; An abrupt decline in kidney function as measured by a rapid decline in creatinine clearance, as defined by the pRIFLE criteria⁹; R- Risk of renal dysfunction, I- Injury to the kidney, F- Failure of kidney function.

Prevalence of acute kidney injury; refers to the proportion of children who have acute kidney injury.

Baseline creatinine; Theoretical creatinine level calculated using Schwartz formula;
Creatinine clearance ml/min = $k \times \text{length (cm)} / \text{serum creatinine (mg/dL)}$. Where $k=0.45$ for infants, $k=0.55$ for children and adolescents.

Hyperbilirubinemia; Total serum bilirubin level of 1.2 mg/dL or more (21 $\mu\text{moles/L}$) or conjugated serum bilirubin of 0.2mg/dL or more (3.4 $\mu\text{moles/L}$)

Hyperparasitemia; presence of malaria parasites 1-9/ single high power field (3+), or 10-100/ high power field (4+).

Hypoxia; resting $\text{SaO}_2 \leq 95$ percent

Intravascular hemolysis; the presence of pallor and jaundice, together with raised serum lactate dehydrogenase.

Sepsis. Suspected infection and the presence of leucocytosis or leucopenia for age, with axillary temperature $>38^\circ\text{C}$ or below 34.5°C , tachycardia (may be absent in hypothermic patients), and at least one of the following indications of altered organ function: altered mental status, hypoxemia, increased serum lactate level, or bounding pulses.

Severe malaria; Plasmodium falciparum parasitemia and clinical, laboratory features as defined by WHO 2010¹. In this study, the presence of one or more of the following clinical or laboratory feature: impaired consciousness or unrousable coma, prostration,

failure to feed, multiple convulsions, deep breathing, respiratory distress (acidotic breathing), circulatory collapse or shock, systolic blood pressure < 50 mm Hg in children, clinical jaundice plus evidence of other vital organ dysfunction, haemoglobinuria, severe normocytic anaemia (Hb < 5 g/dl), hyperparasitaemia, hyperlactataemia (lactate > 5 mmol/l).

Cerebral malaria: Unconscious child with Blantyre coma scale ≤ 2 30 minutes after administration of intravenous 25% glucose, and with asexual forms of Plasmodium falciparum on a blood smear microscopy.

Volume depletion; A condition that results in any degree of dehydration, as assessed by parameters in Appendix VI.

ABSTRACT.

Background: There were 219 million malaria cases reported in 2010, and 660,000 deaths of which 91% were in Sub Saharan Africa. Disordered renal physiology in patients with severe malaria is associated with 45% mortality. There is limited data on occurrence of acute kidney injury among children with malaria. In addition, the case definition for acute kidney injury has varied in previous studies. This study described the prevalence, clinical characteristics and severity of acute kidney injury among children with severe malaria in a resource limited setting.

Study objectives: The study objectives were to determine the prevalence of acute kidney injury among children with severe malaria at Mulago using the pRIFLE criteria, describe their clinical characteristics, describe the severity of acute kidney injury in these children admitted in Mulago.

Methodology: This was a cohort study done at Mulago Hospital acute care unit. Children aged 6 months to 12 years with severe malaria were recruited between March 2013 and June 2013. Blood was drawn for serum creatinine levels to determine the prevalence and severity of acute kidney injury according to the pRIFLE criteria. Clinical assessment and serum creatinine were repeated until seven days since admission. Data was collected on semi-structured questionnaires.

Results: The prevalence of acute kidney injury in the study was 19.9%.. According to the pRIFLE criteria, 74% fulfilled pRIFLE risk, 14% fulfilled injury, 12% fulfilled failure criteria.

Of the clinical characteristics, all children with cerebral malaria and shock had acute kidney injury. Within seven days, 76.3% of those fulfilling pRIFLE-risk no longer

fulfilled the RIFLE criteria, and 57.1% in those having pRIFLE-injury no longer fulfilled pRIFLE, while all in the failure group still fulfilled pRIFLE.

Conclusion: One in five children with severe malaria has acute kidney injury, with most fulfilling the pRIFLE-risk criteria. A child with cerebral malaria, or with shock, must be managed with a high index of suspicion for acute kidney injury.

A child with more severe forms of AKI (pRIFLE-Failure) may not show improvement within seven days.

Recommendations: The use of pRIFLE criteria in the management of children with acute kidney injury and severe malaria is recommended in our setting to decrease the morbidity and mortality due to malaria. A follow up study beyond seven days is recommended to determine the long term outcomes of acute kidney injury, like chronic kidney disease.

CHAPTER ONE

1.0 Introduction

1.1 Background.

Malaria is still a major cause of mortality and morbidity, with 219 million cases reported in 2009 and 660,000 deaths, 91% of which are in Sub-Saharan Africa according to WHO World Malaria Report 2010⁽¹⁾ 85% of these deaths occur among children under 5 years of age and within the first 24 hours from severe malaria, before the full benefits of effective antimalarial treatment can be obtained⁽²⁾ Severe malaria, according to WHO, is defined as the presence of Plasmodium falciparum asexual parasitemia and the presence of one or more clinical or laboratory features, with no other cause of symptoms.⁽³⁾

Renal failure is one of the features of severe malaria, and it is defined as a serum creatinine level of $> 265 \mu\text{mol/l}$ in the WHO malaria report 2010.⁽³⁾

Renal failure among adult patients with malaria has been widely described. Among children with severe malaria, few studies have been done. The prevalence of acute renal dysfunction among children with malaria in Africa has been described to range between 13.5% to 42.5% using various parameters like serum creatinine above $62 \mu\text{mol/L}$ ⁽⁴⁾, the protease inhibitor serum cystatin c,⁽⁵⁾ and urine output⁽⁶⁾ and among different study populations of children. In Mulago hospital, the prevalence of acute renal failure was described to be at 18.2% using the WHO definition of serum creatinine $>265 \mu\text{mol/L}$.⁽⁷⁾

Direct comparisons between these populations is difficult as the different studies used varying methods and definitions of renal dysfunction, and has resulted in varying recommendations concerning clinical management. Mortality among these children has been found to be as high as 45%.^(8,9)

A new definition of renal failure, now known as acute kidney injury (AKI), has been proposed.⁽⁸⁾ This definition of AKI is known as the RIFLE criteria (**R**isk of renal dysfunction, **I**njury to the kidney, **F**ailure of kidney function, **L**oss of kidney function, **E**nd stage renal disease). RIFLE criteria aims to standardize the definition of acute renal dysfunction/acute kidney injury by stratifying patients based on the changes in serum creatinine from baseline and/ or an abrupt decrease in urine output,⁽¹⁰⁾ and has been found to be highly sensitive in detection of acute kidney injury.

The pRIFLE criteria in children considers the estimated creatinine (eCCl), that is calculated using the Schwartz formula. Serum creatinine in children is dependent on body mass, which is directly related to height and age of a child. Schwartz formula is therefore appropriate for use in children. ($eCCl = K \times \text{length in cm} / \text{plasma creatinine in mg/dL}$)⁽¹¹⁾. This formula has been validated as a good means to estimate creatinine clearance in paediatric patients, in whom its measurement by 24 hour urine collection is challenging⁽¹²⁾. However, it has not been validated for African children, who were considered to have a less muscle mass compared to their North American counterparts⁽¹³⁾. With the Schwartz formula that estimates creatinine clearance, as the glomerular filtration rate falls, creatinine secretion is increased, and the rise in serum creatinine is less.

1.2 Problem Statement.

Malaria is a leading cause of mortality in Africa. Mortality among children with malaria and acute kidney injury (AKI) is up to 45%, with more severe forms of acute renal

dysfunction associated with a worse outcome, despite more effective antimalarial treatment, the artemisinin derivatives. ⁽²⁾

This high morbidity and mortality could be a result of the varying definitions of acute kidney injury used in clinical trials, making the development of diagnostic and prognostic criteria difficult ^(8, 45). This results in delays in clinical diagnosis and management of AKI among children with severe malaria.

There is paucity of data on the prevalence, severity, and clinical characteristics of acute kidney injury among children with severe malaria in Sub Saharan Africa. In Uganda, even less is known.

Delay in diagnosis of AKI results in progression of AKI to more severe forms that are refractory to fluid resuscitation ⁽⁴⁶⁾. Such patients with severe AKI will require renal replacement therapy, which is not widely available in a resource limited setting like Mulago Hospital.

Children receiving intravenous quinine for severe malaria require dose adjustment by a third in the presence of AKI, ⁽³⁾ and nephrotoxic drugs like Non Steriodal Anti-Inflammatory Drugs commonly used as antipyretic, and gentamycin a first line antibiotic for pneumonia which is a common co-morbidity need to be avoided in the presence of AKI ⁽⁴⁶⁾

1.3 Justification

The worldwide morbidity associated with acute kidney injury (AKI) is poorly known because of underreporting, regional disparities, and differences in definition and study populations especially in Sub Saharan Africa. The studies done so far have not used a

standardized definition of acute kidney injury as recommended by the Acute Dialysis Quality Initiative (ADQI) group.

Severity of AKI in Mulago among children with malaria is not documented, and yet it is important to describe it in this endemic area.

This study therefore aims to describe the prevalence, severity of AKI, clinical characteristics of children admitted in Mulago hospital with severe malaria and AKI. The RIFLE criteria has good sensitivity for the less severe forms of AKI. This will enable clinicians to intervene early and prevent progression to more severe form of AKI, of which the treatment is renal replacement therapy that is not widely available in Mulago.

1.4 Objectives

1.4.1 General Objectives.

To determine the prevalence, severity of acute kidney injury among children with severe malaria admitted in Mulago Hospital, and to describe the difference in clinical characteristics among children with severe malaria and AKI, and those without AKI.

1.4.2 Specific Objectives

Primary Objectives

1. To determine the prevalence of acute kidney injury among children with severe malaria admitted in Mulago hospital.
2. To determine the severity of acute kidney injury among children with severe malaria admitted in Mulago hospital.

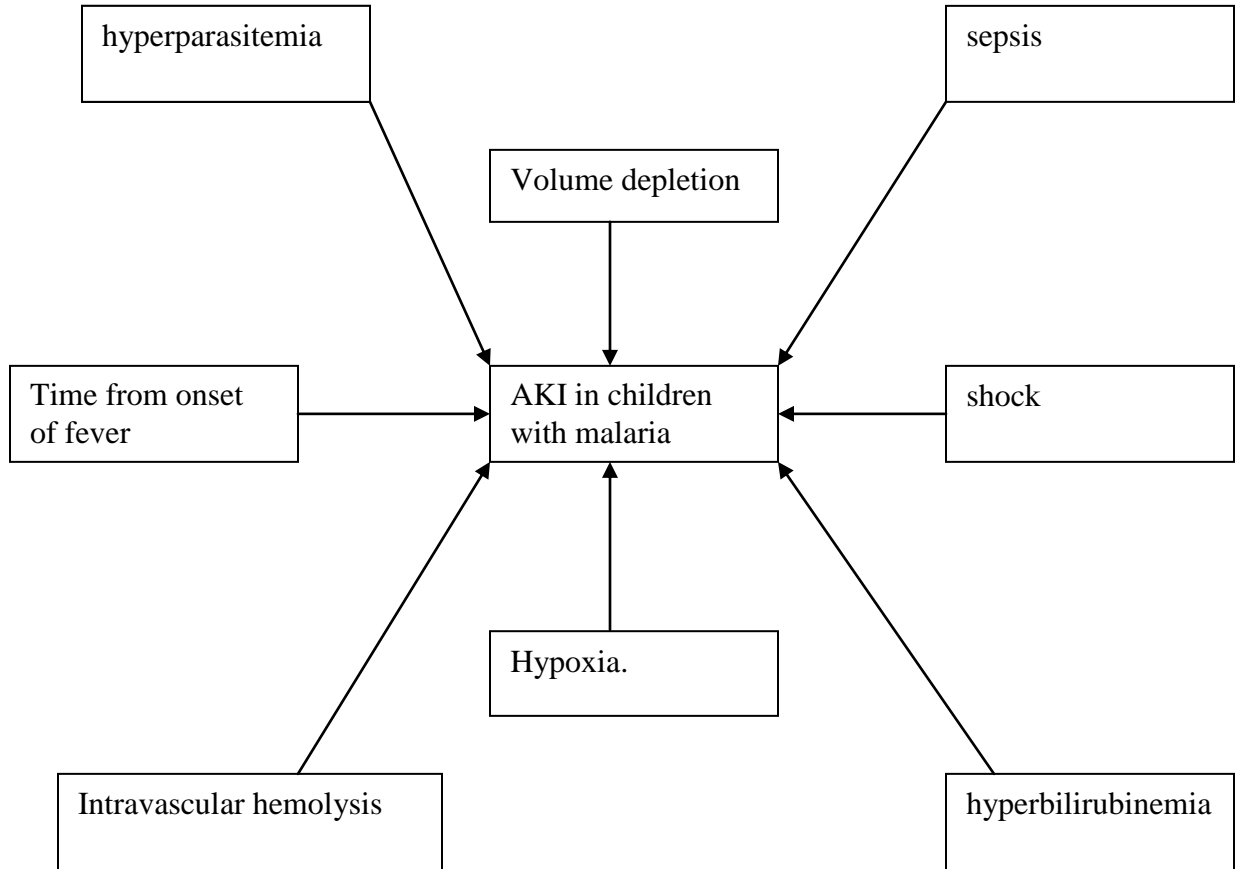
Secondary Objectives

1. To describe the difference in clinical characteristics of children with severe malaria and AKI and those without AKI.

1.5 Research Question

1. What is the prevalence of acute kidney injury among children with severe malaria admitted in Mulago hospital?
2. What is the severity of acute kidney injury among children with severe malaria admitted in Mulago hospital?
3. What is the difference in clinical characteristics of children with severe malaria and AKI, and those without AKI?

1.6. Conceptual Framework.



CHAPTER TWO

2.0 Literature Review

2.1 Introduction

Renal dysfunction is commonly a result of indirect factors, like mechanical, immunological and humoral factors, among people with Plasmodium falciparum infection.⁽¹⁴⁾ Pre-existing renal dysfunction may also worsen during an infection with Plasmodium falciparum. Extrarenal manifestations of renal dysfunction include hypervolemia, euvolemia, hypovolemia, hyponatremia, hypokalemia, hypocalcemia, hypernatremia, hyperkalemia hypophosphatemia, while the renal manifestations include hemoglobinuria, methemoglobinuria, myoglobinuria, mild glomerulonephritis (proteinuria with mild urinary sediment changes) acute nephritic syndrome, nephrotic syndrome and acute renal failure.

2.2 Acute Kidney Injury And Malaria.

2.2.1 Pathophysiology of AKI in malaria.

Malaria causes its renal effects through mechanical, humoral and immunological processes.⁽¹⁴⁾ Mechanical processes of cytoadherence, rosetting, and sequestration all result in impaired blood flow to the kidney, reduced oxygen supply, impaired mitochondrial ATP synthesis, and stimulates cytokine production.⁽¹⁵⁾ Cytoadherence occurs when red blood cells (RBCs) that are infected with the parasite in the late stages adhere to the capillary and post capillary venular endothelium in the microvasculature.⁽⁸⁾
¹⁵⁾ Rosetting is adherence of non-parasitized cells to the parasitized cells. As a result of these two processes, the parasites are sequestered in various organs/ deeper tissues, evading the spleen that clears these parasites. The above processes are facilitated by

tumor necrosis factor-induced expression of adhesion molecules I-CAM, ELAM-1, VCAM-1, and CD36.⁽¹⁶⁾

Immunological effects of malaria on the kidneys is mediated by cytokines like tumor necrosis factor α , IL-6, and serum soluble CD-14, which have been found to be higher in subjects with malaria and ARF compared to those with septicemia and normal subjects.⁽¹⁷⁾ These cause release of reactive oxygen species from neutrophils that directly damage the kidney cells, stimulate the expression of cellular adhesion molecules (which result in blockade of renal microvasculature, and reduction of perfusion), induce lactic acidosis, cause release of vasoactive mediators, and plasma leakage. These all cause hypovolemia and reduced renal perfusion.^(18, 19)

Humoral processes involved in the pathogenesis of renal dysfunction in malaria patients include hypercatecholaminemia following sympathetic stimulation and stimulation of adrenal gland by kinin. This results in renal vasoconstriction, increased vascular permeability, hypovolemia and compromised renal blood flow.^(14, 20)

Malaria can also worsen pre-existing renal disease through the same mechanisms mentioned above.

2.2.2 Clinical Significance Of Renal Dysfunction In Malaria.

Malaria affects all ages, but the multiple-systemic impairments vary according to age. *Kocher et al* in a prospective study to describe the clinical features of 303 children hospitalized with malaria, found some manifestations like cerebral malaria, respiratory distress, and renal dysfunction more common in children 5-10years of age.⁽²¹⁾ In a descriptive study performed in a Karachi hospital to identify clinical features of severe malaria and their association with adverse outcome, *Ahmed et al* found renal failure

present only in the group of children with malaria that died, and not in the survivor group⁽²²⁾.

In an observational study of 624 children aged 1 to 9 years with cerebral malaria in The Gambia by *Jaffar et al*, those with raised serum urea above 6.4 mmol/L were more likely to die compared to those with lower levels (Odds ratio 2.8)⁽²³⁾. The mortality rate among patients with malaria and acute renal failure is 42% among adults in areas where malaria infection is epidemic⁽²⁴⁾ and 45% among children in areas of endemic transmission, as described by *Soni et al* in a retrospective case series study in Durban.⁽²⁵⁾ Majority (79.8%) of deaths due to acute renal failure associated with falciparum occurred within the first 48 hours^(23, 24).

Ahmed et al, in a descriptive study in Karachi to identify clinical features of severe malaria and their association with adverse outcome,, found positive correlation between duration of illness and impairment of renal function, with patients admitted for greater than 7 days being more likely to have derangements in urea and creatinine⁽²⁶⁾

The management of renal dysfunction in children with malaria requires rapid assessment, appropriate antimalarial therapy, fluid replacement, renal replacement therapy, supportive therapy and avoidance of nephrotoxic drugs⁽²⁷⁾. Intravenous quinine dose should be reduced by one third in renal dysfunction⁽²⁷⁾

Renal blood flow and perfusion should be maintained by infusion with fluids, which should be slow and titrated against central venous pressures because of the vulnerability of ARF patients for post-transfusional volume overload^(27, 28). These patients should be carefully monitored for volume overload. Due to hypercatabolic state in patients with malaria and acute kidney failure, renal replacement therapy should be immediately

performed for those with rapidly increasing creatinine concentration ^(20, 29). Diuretics, commonly used to increase urine output in these patients, have not been proven to improve renal function. ACE inhibitors, NSAIDs, aminoglycosides, cephalosporin, and other nephrotoxic drugs should be avoided.

2.2.3. Prevalence Of Renal Dysfunction Among Children With Malaria

Worldwide occurrence of malaria and acute renal dysfunction is between 0.6 and 60% depending on the region ⁽³⁰⁾, but is associated with 45% mortality ^(8, 31). In endemic areas, renal dysfunction occurs in more than 4% of patients.

Ladhani et al in a chart review in East London found 3/211 (1.42%) children below 16 years, majority non immune, with documented malaria had renal failure according to WHO criteria. (decreased urine output and serum creatinine above 265 μ mol/L)⁽³²⁾.

Radha et al in a prospective study done in India found 53/374 (14.2%) children with renal failure defined according to WHO as urine output <0.5 mL/Kg/hr and serum creatinine >1.5g/dL. In this study, renal dysfunction was not significantly associated with mortality.⁽³³⁾

In a randomized clinical trial comparing the efficacy of artemether and quinine in Northern India, 8.7% of the 46 children aged up to 14 years had renal failure at baseline, also according to WHO definitions. Children with renal failure were treated with artemether, and ¾ of these children died.⁽³⁴⁾

In Sub Saharan Africa, *Weber et al* in The Gambia compared cases of cerebral malaria and cases of mild malaria with controls having fever without malaria. Using serum creatinine alone as a measure of kidney function, they found 25% of those with cerebral malaria and 4% of those with mild malaria had raised serum creatinine above the age

specific cut-off of 62 μ moles/L. None of the control had raised serum creatinine. This however was not associated with increased mortality.⁽⁴⁾

Martland et al in Kilifi Kenya during a retrospective study aimed to study the role of hypovolemia in childhood severe malaria, found 20.4 % children had raised serum creatinine greater than 80mmol/L, with a fatality rate of 26%.⁽³⁵⁾

The protease inhibitor cystatin C that is independent of gender and muscle mass and therefore a more sensitive marker of acute renal dysfunction than creatinine was used by Burchard et al in Ghana to compare 78 children in Ghana aged 5-59 months having uncomplicated malaria with 23 children in a fever group. In the malaria group, 17% had raised cystatin C compared to none in the fever group.⁽⁵⁾

Ifeoma et al retrospectively reviewed data of 211 children in Nigeria, where malaria was associated with 13.7% of the cases of renal failure, defined as rising serum creatinine and urea.⁽⁶⁾

Nabachwa et al in a cross sectional study in Mulago Hospital in 2003 found raised serum creatinine in 18.2% of 99 children with severe malaria, while none of the 19 children in the control group had raised creatinine. She recommended a similar study should be done among children with simple malaria, and also to determine the severity of renal impairment in children with malaria.⁽⁷⁾

None of these previous studies have used the RIFLE criteria, which aims to standardize the definition of AKI by categorising patients based on changes in serum creatinine from baseline and/ or an abrupt decrease in urine output.⁽¹⁰⁾

2.2.4. Factors Associated With Acute Renal Dysfunction And Malaria

Acute renal dysfunction has been associated with volume depletion, intravascular hemolysis, heavy parasitemia, hyperbilirubinemia, hypotension, sepsis, and disseminated intravascular coagulation⁽³⁶⁾. *Sheiban et al*⁽³⁷⁾ in 1996 compared characteristics of children with malaria between the group that died and the group that survived. They found mean values of plasma creatinine 645µmoles/L versus 104µmoles/L, serum bilirubin 2.1mg/dl versus 1.2 mg/dl, systolic Bp 50mmHg versus 90 mmHg, diastolic Bp 20mmHg versus 60mmHg, hemoglobin level 5.3g/dl versus 8g/dL in the two groups respectively. *Maheswari et al* found sepsis to be associated with acute renal failure. *Junejo Abdul et al* found hyperbilirubinemia in 71.7%, sepsis in 15.2% patients with acute renal failure and malaria⁽²⁶⁾

Age

In a prospective study done over a period of 15 months in India to investigate the whole spectrum of severe illness in 303 children admitted with falciparum infection, renal dysfunction was present in 30.4% of children. This proportion was only 6% among children aged 0-5 years, compared to those aged 5-10 years of age where the proportion was 14.7%⁽²¹⁾

Volume depletion.

Volume depletion was identified as a dominant cause of acute renal failure in 72.8% of 81 people with malaria by *Maheshwari et al* in a study of the spectrum of renal disease in malaria⁽³⁸⁾. This results from cellular damage and increased vascular permeability caused by reactive oxygen species. It can be caused by persistent fever, profuse sweating, inadequate fluid intake, vomiting and loose motions⁽²⁵⁾. Dehydration should be managed

with 0.9% saline, or 5% dextrose saline, with monitoring of jugular venous pressure, blood pressure, peripheral pulses, skin turgor and urine volume^(2, 25). *Sheiban et al*⁽³³⁾ found that among children with acute renal failure and malaria, those with low blood pressure at presentation died.

Hyperbilirubinemia.

Excessive intravascular hemolysis results in more of unconjugated hyperbilirubinemia, than direct hyperbilirubinemia from cholestasis, and has been found to occur in malaria associated with acute renal failure^(1, 19, 26, 36). Hyperbilirubinemia has been associated with reduced GFR and a worse outcome (Day et al). It does not require any specific treatment, except in situation of severe hemolysis associated with severe anemia⁽²⁵⁾.

Intravascular Hemolysis.

Intravascular hemolysis contributes to hyperbilirubinemia⁽³⁸⁾ and in children with G6PD deficiency results in intractable renal failure.⁽³⁹⁾

Hyperparasitemia.

Ekeanyanwu et al in a study to estimate kidney function parameters in 45 Plasmodium falciparum infected children found that malaria parasitemia was positively correlated with serum creatinine.⁽⁴⁰⁾

Sepsis

Sepsis results in the release of inflammatory cytokines tumor necrosis factor, IL-6, which contribute acute kidney injury⁽¹⁴⁾.

2.3 Rife Criteria

The RIFLE criteria (acronym for **R**isk for renal dysfunction, **I**njury to the kidney, **F**ailure of the kidney, **L**oss of kidney function, and **E**nd stage renal disease) is a new definition for acute renal failure proposed by the Acute Dialysis Quality Initiative(ADQI) group during a consensus meeting in 2004⁸. The RIFLE aims to standardize the definition of acute kidney injury by categorizing patients based on changes in serum creatinine from baseline and/ or an abrupt decrease in urine output⁸. It contains three level of renal dysfunction(R, I, F) and two outcomes (L and E).

The RIFLE criteria has been validated in adult patients presenting with tropical acute febrile illnesses. Gopal Basu *et al* in a prospective study to determine the incidence, severity of AKI based on the RIFLE classification and its association with mortality and the requirement for renal replacement therapy among 367 adults found an increased risk of mortality of 6.9, 20.2 and 25.6 for the RIFLE-Risk, RIFLE-Injury and RIFLE-Failure groups respectively⁽⁴¹⁾. A literature search by Ricci *et al* on the RIFLE criteria and whether outcome progressively worsened with severity of AKI found that the relative risk for mortality compared to non-AKI subjects was; R=2.40, I= 4.15, F= 6.37⁽⁴²⁾.

A modified pRIFLE, proposed by Akcan-Akiran *et al*, has been recommended for pediatric patients ⁽²⁹⁾, in which estimated creatinine clearance is calculated according to the Schwartz formula ⁽²⁹⁾ Risk is estimated creatinine clearance decreased by 25%, or urine output less than 0.5ml/Kg/hr for 8hours. Injury is estimated creatinine clearance decreased by 50%, or urine output less than 0.5mls/kg/hr for 16 hours. Failure is estimated creatinine clearance decreased by 75% or urine output less than 0.3mls/kg/hr for 24 hours or anuric for 12 hours. Loss is persistent failure for more than four weeks.

End stage renal disease is persistent failure for more than three months. The presence of AKI in the study by *Akcan-Akiran* et al was not an independent risk factor for mortality, but the patients who had no improvement in renal function within 48 hours of admission were at a higher risk of requiring dialysis.

The sensitivity of the RIFLE criteria decreases as one moves through the categories R, I, F, L and E, while the specificity increases in the same direction, making it good for early detection of acute kidney injury.⁽¹⁰⁾ The RIFLE criteria can also be applied to acute-on-chronic renal failure.

CHAPTER THREE

3.0 Methodology

3.1 Study setting

The study was carried out from the Acute Care Unit (ACU) of Mulago hospital. Mulago hospital is Uganda's national referral hospital. Mulago National Referral Hospital is the teaching hospital of the Makerere University College of Health sciences. The hospital serves patients from within, and around Kampala, and other neighboring districts.

The paediatrics department has a total of seven specialized wards. The Acute care unit is the emergency ward where all medical in-patients are first admitted and resuscitated and then transferred to the other wards. Patients are admitted throughout the whole day. ACU is run by a team of paediatricians, senior house officers, intern doctors and nurses. From the ACU, children with severe malaria were admitted either to Haematology ward, or Stanfield ward (infectious diseases ward). Some patients with renal failure were admitted in the paediatric intensive care unit, and later transferred to the Renal ward, where the patients with renal disease are managed under the care of the renal team.

3.2 Study Design

This was a descriptive cohort study done to determine the prevalence, severity of acute kidney injury among children with severe malaria admitted in Mulago Hospital, and to describe the difference in clinical characteristics of AKI among children with severe malaria and those without AKI.

3.3 Study Population

Target Population.

All children between 6 months and 12 years admitted to the Acute Care Unit (ACU) Mulago.

Accessible Population.

Children 6 months of age to 12 years with severe malaria to the ACU Mulago Hospital.

3.4 Selection Criteria

3.4.1 Inclusion Criteria

1. Children aged 6 months to 12 years
2. Children who had severe malaria (as defined by WHO 2010)
3. Patients whose parents or guardians provided informed consent, and when conscious children 8 years and older provided assent to participate in the study.

3.4.2 Exclusion Criteria

1. Children who had severe acute malnutrition (weight for height <-3 Z score, mid upper arm circumference <11.5cm, presence of pitting pedal edema)

3.5 Sample Size Estimation.

Prevalence Sample Size Estimation.

Sample size for a study to estimate a parameter from a dichotomous variable i.e. the presence or absence of AKI, using the Kish Leslie formula, sample size was

$$N = \frac{Z^2 P (1 - P)}{W^2}$$

N was the sample size required, $Z\alpha$ was the standard normal value corresponding to 95% level of confidence, P was the prevalence of 19% (Nabacwa et al), W was the width of the confidence interval set at 5%.

$$N = \frac{1.96^2 \times 19 \times (.81)}{.05^2} \quad N = 237$$

3.6 Sampling Procedure.

The study subjects were enrolled consecutively until the required sample size was achieved.

3.7 Study Variables

The dependent variable was serum creatinine of a child aged 6 months to 12 years.

The independent variables were: age, sex, duration of fever, impaired consciousness or unrousable coma (Cerebral malaria), prostration, failure to feed, multiple convulsions, deep breathing, respiratory distress (acidotic breathing), circulatory collapse or shock, systolic blood pressure < 50 mm Hg in children, clinical jaundice plus evidence of other vital organ dysfunction, haemoglobinuria (tea coloured urine), severe normocytic anaemia (Hb < 5 g/dl), hyperparasitaemia, hyperlactataemia (lactate > 5 mmol/l).

3.8 Study Procedure

Children aged 6 months to 12 years attending Acute Care Unit, Mulago Hospital were screened by a member of the research team. These children already had a blood smear microscopy done by Field stain, by the laboratory technician.

A two step enrolment was done. Verbal consent was initially obtained for a child who required resuscitation. A child whose caregivers consented was then subjected to the following procedures.

Clinical History

Standard emergency care was provided for severe malaria (appendix 8). A detailed history was taken for presenting complaints of fever, convulsions, altered mental state, cough, fast breathing, grunting, passage of tea colored urine, reduction of urine amount, ability to drink, presence of vomiting or diarrhea, yellow discoloration of the eyes, flank pain, presence of bleeding, intravenous fluid use prior to admission in Mulago, and prior NSAID use (appendix II).

Physical examination

A thorough physical examination conducted as soon as the patient was stabilized (appendix 2) to determine the weight, height, mid upper arm circumference, temperature, blood pressure, pulse and respiratory rates, capillary refill, oxygen saturation, presence of dehydration, the presence of anaemia, and presence of oedema. Cardiovascular examination done for the presence of bounding pulse, a 3rd heart sound, a cardiac murmur. A respiratory examination was done for respiratory crackles. Abdominal examination for presence of tenderness in the renal angles, hepatomegaly and splenomegaly. A neurologic exam performed to determine the Blantyre coma scale.

Anthropometry.

Weight.

Weight was taken before any treatment was administered, with the child wearing only his/her under pants, on a well calibrated seca® 761 mechanical scale, and the reading made to the nearest 100 grams. Infants were weighed in the weighing pants attached to a scale.

Height.

Height was taken for those children who were 2 years and above, and were able to stand, using a stadiometer. This was one made locally with a tape attached to a board, which had a fixed headpiece and a mobile footpiece. Those younger than 2 years, or those too sick to stand had their length taken using a stadiometer placed flat on a table. This procedure required 2 people; one to ensure that with the feet together, the heels and knees touch the board, and the other to ensure the head and back are in position against the board with eyes looking straight ahead. The footpiece or headpiece was then moved to touch the child, and the reading taken for length and height respectively, and recorded to the nearest centimetre.

Mid Upper Arm Circumference.

Mid upper arm circumference (MUAC) was taken using a coloured centimetre MUAC tape. With the elbow flexed, the zero mark of a tape was placed at the tip of the shoulder, and the tape placed against the arm all the way to the elbow. The mid-point reading was considered as the mid upper arm point, and this was marked with a pen. The arm was then straightened and the MUAC tape put around the mid-point to read the MUAC to the nearest 0.1 centimetre.

Blood Pressure Measurement.

Blood pressure (BP) measurement was done using Reister Babyphon® machine, which has three velcro paediatric cuff sizes to fit infants, toddlers and older children. The proper cuff width was selected by ensuring the BP cuff width is almost half the circumference of the arm, and the BP cuff long enough to encircle the arm. With the child in sitting position, the first Korotkoff sound and the fifth Korotkoff sounds were recorded as the systolic, and the diastolic BP measures. The measurement was repeated and an average of the two was recorded.

Respiratory And Pulse Rates.

The respiratory rate was counted in a calm child for one whole minute, and so was the radial pulse. The measurements were repeated, average taken, which were then recorded. Oxygen saturation was measured using an oxymeter placed on the child's finger, and the value recorded. The child was then bled for tests as described below.

3.9 Laboratory Investigations.

Collection Of Samples.

Blood was collected from a peripheral vein. The skin was cleaned with 70% alcohol, and 6ml was collected into a sterile syringe. 3 ml was transferred to EDTA bottle for complete blood count and parasite densities, while the remaining 3 ml were sent for renal and liver function tests.

3.9.1 Blood Smear For Malaria.

Giemsa Stain 10%.

For children who initially had a positive blood smear for malaria on Field stain and with severe malaria, a second test for malaria was performed immediately using 10% Giemsa

stain for quality control. This test was performed by a laboratory technologist in ACU. A smear was flooded with 10% Giemsa stain for 15 minutes. It was then washed with water until no stain was draining from the smear. The smear was air dried, and 20 fields were examined under oil immersion, x100 power. A child who had both the Field and Giemsa stains positive for malaria, was considered to have a positive blood slide for malaria.

The parasite densities were also counted by the laboratory technologist in ACU, by counting the parasites per 200 white blood cells. A second lab technologist, based in the molecular laboratory in Mulago examined the slides of 30 patients for quality control.

3.9.2 Complete Blood Count And Chemistry.

Samples for complete blood counts and renal function tests were collected and analyzed within 8 hours in the day time. For those samples collected at night, they were stored at 2°C to 4°C before they could be analyzed the next day.

Complete blood counts were done at Mulago using an automated CBC machine (Nihon Kohden Celltac, Haematology analyser, Japan), by a laboratory technologist, while liver and renal function tests were done using Roche Cobas C 501 analyser.

Serum creatinine was repeated on day 1, 4 and 7 depending on the length of stay on the ward, to detect a rise or a fall, that would point to worsening or improvement in kidney function respectively. A blood smear for malaria parasites was repeated on day 1 for all children, usually after 24 hours of either intravenous quinine or artesunate.

3.10 Patient Management.

Written informed consent/ assent were obtained when the child was stable, and had received initial treatment. The study was introduced to the care taker, and the procedure was explained as well. The risks to the child, rights of the patient, as well as voluntary participation in the study was clearly explained to the care taker of the child. Any questions the care taker had were answered in the simplest, yet most detailed way possible. The consent form was read to the care taker, and understanding was verified, before written informed consent was obtained.

The theoretical baseline creatinine was calculated by assuming a normal GFR for age (appendix IV) and applying Schwartz formula for the purpose of determining the change in subsequent creatinine measurements from baseline ⁽⁸⁾

$$\text{Normal GFR for age} = K \times \frac{\text{Length (cm)}}{\text{theoretical Serum creatinine (mg/dL)}}$$

where the constant K=0.45 for infants, and 0.55 for children and adolescents.

Subsequent GFR were calculated using the Schwartz formula and the measured serum creatinine values taken on days 1, 3 and 7.

Those children found to have acute kidney injury according to the Schwartz formula were managed according to the guidelines (see appendix VIII), with fluid and electrolyte balance, as well as close monitoring. Those children that still had acute kidney injury after 48 hours were admitted to the renal unit, for further management, and were followed up until discharge or unit seven days, whichever came first. Co-morbidities were managed according to available protocol.

Abdominal ultrasound was done for children fulfilling the RIFLE criteria for acute kidney injury once they were resuscitated, to determine the presence of kidneys, kidney size, a description of the renal parenchyma, and evaluation for the presence of urinary tract obstruction. All children with severe malaria were reviewed daily up to seven days post-admission, or until discharge, whichever came earlier.

3.11 Study Instrument.

A structured questionnaire was used to collect information. It was pretested to determine appropriateness prior to the actual data collection. The questionnaires were administered by the principle investigator with the help of the research assistant (medical officers). The questionnaires collected information on socio-demographic characteristics (age, sex, and address), clinical history of presenting symptoms, duration of illness, as well as a record of the vitals, anthropometric measurements, and results for creatinine, bilirubin level, lactate dehydrogenase, white cell count, and blood smear for malaria.

3.12 Radiological Investigations.

Abdominal ultrasound to determine kidney size were done at the Mulago Hospital radiology unit, by a trained radiographer, using model Philips HD 7 2007 for children with raised serum creatinine who fulfil the RIFLE criteria once the child was clinically stable.

3.13 Data Management

3.13.1 Data Collection

A pretested and precoded questionnaire was used to obtain information. Data was stored in a secure cupboard.

3.13.2. Data Analysis

The data was entered using Epi data version 3.1. Soft ware package. Data was analyzed using STATA version 10 by the principle investigator, with the help of a statistician.

Continuous variables were analyzed using means, medians and standard deviations, while categorical variables into frequencies, proportions and percentages. The data was summarized in tables.

The variables included in the analysis include, serum creatinine, age, sex, duration of fever, repeated convulsions, respiratory distress, shock, impaired consciousness/ unarousable coma, clinical jaundice, tea coloured urine, severe anaemia, hyperparasitemia.

3.13.4 Quality Control

Two medical officers were trained as research assistants before the commencement of the study. The questionnaire were pretested for the suitability of questions and necessary adjustments made. Questionnaires were checked every day for completeness by the principle investigator. There were standard operating procedures for the collection of specimens. All blood tests were carried out in the haematology and microbiology laboratory at Mulago hospital. These laboratories are accredited by

3.13.5 Ethical Considerations

Approval to conduct the study was sought from the School of Medicine Research and Ethics Committee and Uganda National Council of Science and technology.

Written informed consent was sought from the care takers of all the study participants, management of the children that did not consent were not affected and the participants had the freedom to withdraw from the study.

3.13.6 Dissemination Of Results

The results from the study were shared with the paediatrics department, Makerere University College of Health sciences, Mulago hospital administration, Ministry of Health, Sir Albert COOK library and publications will be made in peer reviewed journals.

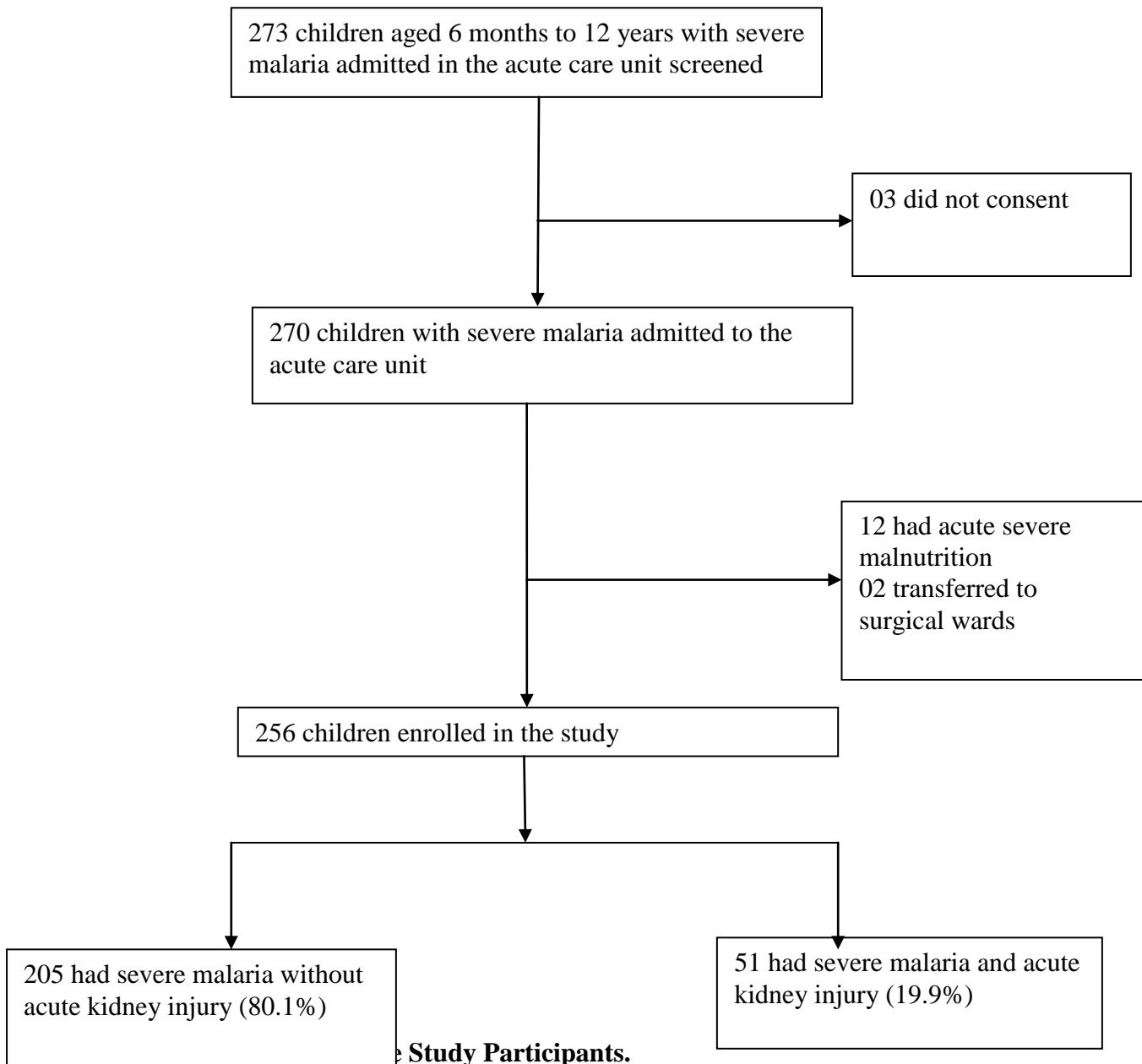
CHAPTER FOUR

4.0 Study Findings

4.1 Description of Study Participants

During the study period of February to June 2013, a total of 256 children were recruited into the study and observed for the development of AKI. (figure 1).

Figure1: Study Profile



Of the children enrolled, 55.9% (n=143) were male and 44.1% (n=113) female. The median age was 33 months (IQR= 18-54months, with majority of the participants under 60 months of age (77.3%, n=198).

Of the children, 59% (n=151) were rural dwellers whereas 41% (n=105) were urban dwellers. Most children (n=250) were reported to be febrile, while 202 reported fever duration of less than a week. Other baseline characteristics of children are shown in **table 1**.

The occupation distribution among the next of kin was as follows: 13.7% (n=35) were salaried employees, 39.5% (n=101) were self-employed, while 46.8 % (n=120) were peasants.

On physical examination, the mean weight was 12.9kg (standard deviation=5.2), median weight was 12kg (IQR=9.5-15kg). Sixty nine point one percent (n=177) had normal Z scores. Common examination findings were fever with 61.3% (n=157), tachycardia 87.1 % (n=223), hepatomegaly 42.6% (n=109), and splenomegaly 41.8% (n=107).

Among the 256 children, the forms of severe malaria that were diagnosed, either alone or in combination with other forms, were as follows; hyperparasitemia 50.3% (n=129), severe anaemia 34% (n=87), hemoglobinuria 23.8% (n=61), repeated seizures 11.7% (n=30), clinical jaundice 19.9% (n=51), cerebral malaria 2.3% (n=6), shock 0.8% (n=2).

Table 1:**Baseline Characteristics Of The 256 Children With Severe Malaria**

Presenting complaint/ physical examination findings	Frequency	Percentage
	N=256	
History of fever	250	97.7
Fever duration < I week	202	79.2
Passed tea coloured urine	98	38.3
Prostration	63	24.6
>2 convulsions in 24 hours	54	21.1
Grunting	50	19.5
Tachycardia for age	223	87.1
Temperature ≥ 37.5	157	61.3
Hepatomegaly	109	42.9
Splenomegaly	107	41.8
Clinical jaundice	95	37.1
Presence of severe pallor	85	33.2
Mild- moderate malnutrition	79	30.9
SpO ₂ <95%	32	13.1
Presence of dehydration	28	10.9
Systolic Bp <50mmHg	6	2.3

4.1.2. Laboratory Findings

Of the 256 children, the mean haemoglobin concentration was 7.16g/dL (SD 3.4), with 65 children (27.4%) having a Hb less than 5g/dL. The mean white blood cell count was $10.99 \times 10^3/\mu\text{L}$ (SD 7.2), with 158 children (66.4%) having high white blood cell count for age. The mean platelet count was $144 \times 10^3/\mu\text{L}$. All of the 216 children who were evaluated for serum lactate dehydrogenase had raised levels above 225mg/dL. Other laboratory characteristics are shown in the table 2.

Table 2

Laboratory Characteristics Of Children With Severe Malaria.

Variable	Mean	Standard deviation
Serum bilirubin $\mu\text{mol/L}$	8.77	15.21
Lactate dehydrogenase	467.34	280.99
Creatinine $\mu\text{mol/L}$	38.10	23.67
Serum Urea mmol/L	6.2	6.2
Potassium mmol/L	7.9	40.4
Sodium mmol/L	132.8	17.4
Chloride mmol/L	105.3	79
GFR ml/min/ 1.73m ²	129.7	46.7

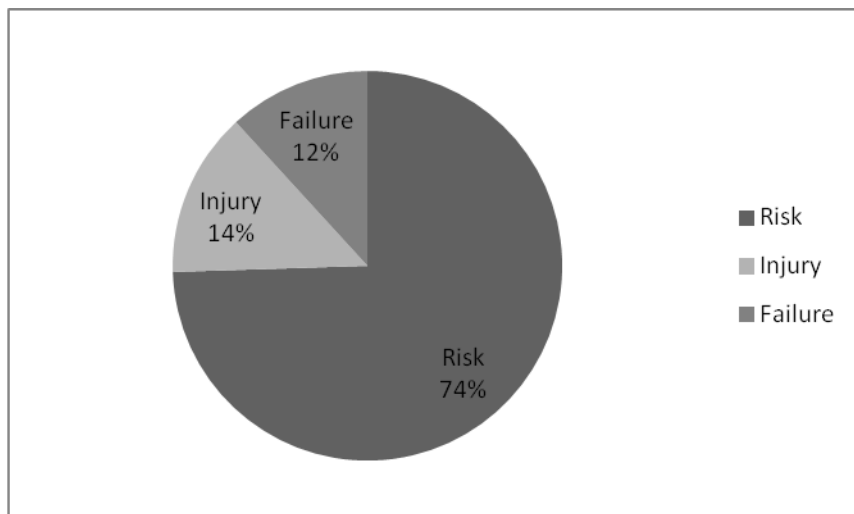
4.2 The Prevalence And Severity Of Acute Kidney Injury.

The prevalence of acute kidney injury was determined by considering three categories of decrease in estimated creatinine clearance according to the modified pRIFLE criteria; Risk-pRIFLE is a decrease by 25%, Injury-pRIFLE is a decrease by 50%, and Failure-pRIFLE is a decrease by 75%.

Fifty one (19.9%) of the 256 participants had severe malaria and acute kidney injury.

Of the 51 children with acute kidney injury, 74.5% (n=38) fulfilled the risk category, 13.7% (n=7) fulfilled the injury category and 11.8% (n=6) fulfilled the failure category of the pRIFLE criteria (figure 3).

Figure 2
Severity Of Acute Kidney Injury



4.3 Clinical Characteristics Of Children With AKI And Severe Malaria.

Of the 51 children with AKI, 44 (86.3%) presented with tachycardia for age, 27 (51.0%) had temperature ≥ 37.5 , 20 (39.2%) had tea coloured urine and 20(39.2%) had severe pallor. Other characteristics of the 51 children with AKI are in the table 3 .

Table 3:
Comparison Of Baseline Characteristics Of Participants Without AKI (N=205) To Those With AKI(N=51)

Variable	Frequency		
	n(%)		
	AKI present n=51	AKI absent n=205	p-value
Passing tea coloured urine	20(39.2)	78(38.2)	0.878
Prostration	18(35.3)	45(22.0)	0.048
Grunting	11(21.6)	39(19.0)	0.682
>2 convulsions in 24hours	10(19.6)	44(21.5)	0.771
Duration of fever>1 wk	8(15.7)	45(22.0)	0.533
Tachycardia for age	44(86.3)	179(87.3)	0.842
Splenomegaly	26(51.0)	81(39.5)	0.137
Temperature ≥ 37.5	27(51.0)	130(63.4)	0.218
Hepatomegaly	23(45.1)	86(42.0)	0.685
Severe pallor	20(39.2)	65(31.7)	0.516
Clinical jaundice	18(35.3)	77(37.6)	0.522
Spo2 <95%	8(15.7)	24(11.7)	0.172
Presence of dehydration	8(15.7)	20(9.8)	0.101

Table 4**Comparing Laboratory Findings Of The AKI(N=51) And Non AKI (N=205) Groups.**

Variable	Mean		
	AKI present n=51	AKI absent n=205	P value
Hb g/Dl	6.63	7.29	0.225
WBC 1000/ μ L	13.64	10.34	0.005
Serum bilirubin μ mol/L	7.79	9.02	0.607
Lactate dehydrogenase	359.95	496.17	0.002
Creatinine μ mol/L	67.52	30.73	<0.001
GFR ml/min/1.73m ²	71.90	143.90	<0.001
Parasite density	67,018.25	105,144	0.113

Potential Risk Factors For Acute Kidney Injury

Among the 51 children with AKI, 100% (2/2) of those with circulatory collapse (systolic BP \leq 50mmHg) and 100% of those with cerebral malaria (6/6) had acute kidney injury. Other potential risk factors for AKI are shown in the table 5 below. None of these were significantly associated with acute kidney injury among children with malaria.

Table 5**Univariable Analysis Of Potential Risk Factors For Acute Kidney Injury**

Factor	Level	Odds Ratio	95% Confidence Interval	Likelihood Ratio P-value
Sex	Male	1	Reference Level (0.40 ; 1.47)	0.42
	Female	0.76		
Age	Above 5 years	1	Reference Level (0.49 ; 2.29)	0.89
	5 years or less	1.06		
Duration of illness	Less than one week	1	Reference Level (0.33 ; 1.74)	0.50
	One week or more	0.76		
Diastolic BP < 50 mm Hg	No	1	Reference Level (0.84 ; 3.24)	0.15
	Yes	1.65		
Intravascular haemolysis	No	1	Reference Level (0.51 ; 2.03)	0.96
	Yes	1.02		
Severe Anaemia	No	1	Reference Level (0.58 ; 2.17)	0.73
	Yes	1.12		
Hemoglobinuria	No	1	Reference Level (0.53 ; 1.98)	0.93
	Yes	1.03		

4.3.1 Renal Ultrasound Findings

Of the 51 children with AKI, the twenty nine had renal ultrasound done that showed 100% had normal kidney shape, contour, position, calyceal system, and absence of renal masses. 2 (6.9%) had abnormal echopattern, 2 (6.9%) had abnormal echogenicity, and 1 (3.5%) had enlarged kidneys.

4.3.2 The Mean Change In Serum Creatinine Within 7 Days Of Admission.

The mean change in serum creatinine among the 51 children with AKI was a fall by 30.63 μ mol/L (SD 45.31, p value <0.001), while the mean change in GFR was an improvement by 41.86 ml/min/1.73m³ (SD 51.99, p value <0.001).

By day seven, 20 children of the 256 study participants were still admitted, 14 (70%) of these had AKI of any category.

Of the 51 children with AKI, 64.7% (n=33) no longer fulfilled the pRIFLE criteria by day seven, 27.5% (n=14) still had AKI by day 7, while 7.8% (n=4) had died. The highest proportion (33.0%) of deaths was in the pRIFLE-Failure group, in which all children still had AKI by day 7. The highest proportion (76.3%) of children that no longer fulfilled the pRIFLE criteria was in the pRIFLE-Risk group. (table 6)

Table 6

Change In pRIFLE Category, And Death Within 7 Days Of Admission Among AKI

AKI Outcome	Frequency	Percentage
Prifle-Failure(n=6)		
Not Fulfilling Prifle	0	0.0
AKI (Any Category) Still Present	4	66.7
Died	2	33.0
Prifle-Injury(n=7)		
Not Fulfilling Prifle	4	57.1
AKI (Any Category) Still Present	2	28.6
Died	1	14.3
Prifle-Risk(n=38)		
Not Fulfilling Prifle	29	76.3
AKI(Any Category) Still Present	8	21.1
Died	1	2.6

CHAPTER FIVE

5.0 Discussion

The aim of this study was to determine the prevalence and severity of acute kidney injury among children aged 6 months to 12 years admitted with severe malaria, to describe their clinical characteristics.

5.1 Prevalence Of Acute Kidney Injury

The prevalence of acute kidney injury among children with severe malaria was 19.9%. This study provided the first documented evidence in East Africa of acute kidney injury, as defined by the RIFLE criteria, among children with severe malaria.

The prevalence in this study was comparable with a study in Mulago by Nabachwa et al, where the prevalence was 18.2%. This study used serum creatinine and glomerular filtration rate that has been used in several similar studies in children.

The prevalence from this study is comparable with other African studies (Weber et al in The Gambia [25% prevalence], Maitland et al in Kenya [20.4% prevalence]). The consistency in these findings could be due to similar participant population of children in areas of high malaria transmission, and the use of serum creatinine as a measure of kidney function. This study however reports a slightly lower prevalence because of the use of glomerular filtration rate that takes into account a child's age and weight. This study has the benefit of having calculated the glomerular filtration rate, a better index of kidney function than serum creatinine. However, due to the increased secretion of creatinine as the glomerular filtration rate falls, thus over-estimation of the GFR, another measure like urine output is recommended to improve the sensitivity of the pRIFLE criteria. When using both, either the urine output criteria or the creatinine criteria that shows the worst possible outcome should be considered⁽⁸⁾.

The use of serum creatinine in the estimation of creatinine clearance has limitations in non-steady state conditions, with overestimation occurring in cases of reduced glomerular filtration rate. Thus, although not a good method to detect AKI, pRIFLE is useful in determining severity, and thus predicting the mortality, and for monitoring the progress of AKI⁽⁸⁾

This study found a higher prevalence compared with a study by Ifeoma et al in Nigeria, due to the use of a more sensitive definition of acute kidney injury, the RIFLE criteria.

5.2 Severity Of Acute Kidney Injury

The severity of AKI by the pRIFLE criteria is useful in predicting mortality rates and the need for renal replacement therapy^(40, 41). In this study, 38 (74.5%) fulfilled pRIIFLE-risk, 7 (13.7%) pRIFLE-injury, and 6(11.8%) pRIFLE-failure. Due to the decreasing sensitivity and increasing specificity as one moves through the categories from Risk, to Injury, to Failure⁽⁸⁾, it is possible that many more patients were categorised as pRIFLE-risk, while some were missed as we consider the pRIFLE-Failure category. This however allows for the p-RIFLE criteria to be used in prompt diagnosis and treatment, hence triggering prompt response for patients who are still within volume responsiveness

5.3 Clinical Characteristics Of AKI Among Children With Severe Malaria

In this study all the children with cerebral malaria, and all the children with shock defined as systolic blood pressure <50mmHg, developed acute kidney injury. This is in keeping with other studies^(33,36).

This is expected considering the pathophysiology of cerebral malaria with sequestration of parasites in the brain. The same mechanism of sequestration in other organs like the kidney could occur, and result in acute kidney injury⁽¹³⁾

Other factors that are potential risk factors like sex, age, duration of illness, intravascular hemolysis, and hemoglobinuria were not significantly associated with acute kidney injury in this study. The sample size in this study was not adequate to describe the risk factors for AKI.

Prostration in the AKI group was at 35.3% (n=18), compared to 22% (n=45) in the non-AKI group. This could have resulted in reduced ability to drink in these children, leading to volume depletion, a known cause of AKI as found in the studies by Maheshwari et al⁽³⁷⁾, and Sheiban et al⁽³¹⁾.

Dehydration was almost two times more common in the AKI group compared to the non AKI group. (15.7% (n=8) versus 9.8% (n=20)). Dehydration is a manifestation of volume depletion. This is similar to a study by Maheshwari et al^(35, 37), where dehydration was associated with AKI.

More children with AKI (15.7%, n=8) presented within 1 week of onset of fever, compared to those without AKI (22% n=45). This could have been due to the more worrying general condition of these children to their caretakers. This is similar to other studies, where children with AKI presented earlier to the hospital^(43, 44).

Fifteen point seven percent (n=8) of children meeting the pRIFLE criteria had oxygen saturation below 95%, compared to 11.7% (n=24) of those without AKI. In children who are hypoperfused or in shock, the readings may be an underestimation of the true oxygen saturation.⁽⁴⁵⁾ In this study, 2 children with shock, had low oxygen saturations, and also had AKI.

Severe pallor was found in 39.2% (n=20) among the AKI group, compared to 31.7% (n=65) of the non-AKI group. This is similar to a study by Zaki et al⁽⁴⁶⁾ that found severe anemia to be significantly associated with AKI in children.

All of the children with cerebral malaria had AKI in this study. This is similar to other studies that have found cerebral malaria to be associated with renal failure ^(5, 45). The prevalence of AKI associated with cerebral malaria is lower in other studies due to the definition of a single serum creatinine cut off for AKI. The same mechanisms of sequestration of red blood cells and platelets occurs in the brain as well as the kidney.

The mean white blood cell counts were 13,640/ μ L in those meeting the pRIFLE criteria compared to 10,340/ μ L in the non-AKI group. Raised white cell count for age was used as criteria for sepsis, together with raised lactate dehydrogenase and tachycardia. Other studies have described sepsis in children with malaria and acute renal failure ^(35, 45).

Serum creatinine was significantly higher in AKI group at 67.52 μ mol/L compared to that in the non-AKI group at 30.73 μ mol/L. The glomerular filtration rate were 71.90 ml/min/1.73m² and 143.90ml/min/1.73m² in the AKI and non-AKI groups respectively. The results are similar to other studies using serum creatinine as a marker of AKI ^(5, 34).

Total serum bilirubin was lower in the AKI group at 7.79 μ mol/L compared to 9.02 μ mol/L the non-AKI group. This is surprising, since most studies have reported hyperbilirubinemia to be positively associated with acute kidney injury ^(25, 35, 45). In this study pre-referral treatment was not captured due to lack of referral notes, and co-morbidities predisposing to hemolysis were not studied, all of which may have affected bilirubin levels.

In this study, lower level of haemoglobin was found in the AKI group compared to the non-AKI group (6.63g/dL and 7.29g/dL respectively), and lower level of mean lactate dehydrogenase (359.95 and 496.17 respectively). The latter implies a lesser degree of intravascular hemolysis in the AKI group, which is not what other studies described ⁽³⁷⁾.

All deaths occurred in the AKI group. The low mortality was due to prompt diagnosis and intervention, having obtained serum creatinine at presentation, and thereafter until seven days or discharge, whichever came first. For AKI patients, stable survival rate is not achieved until after 30-60 days⁽⁴⁷⁾. Having considered up to seven days since admission in this study, it is possible to have under-estimated the mortality.

In this study, those children with more severe forms of AKI (pRIFLE Failure), were still categorised as having a form of acute kidney injury by seven days of admission. This category of patients would have benefitted from renal replacement therapy since serum creatinine levels did not fall within 48hrs. ⁽⁶⁾

This is likely to be due to the continuum of volume responsiveness and non-responsiveness nature of the AKI, with those having pRIFLE-injury and pRIFLE-failure less likely to respond to conservative management. Renal replacement therapy was not available during the time of the study, with patients being managed according to the hospital guidelines on fluid replacement, correction of electrolyte imbalances, and avoidance of nephrotoxic drugs. Additionally, inability to determine underlying pathophysiology in malaria and AKI could have resulted in worse outcome.

The mean change (increase) in the glomerular filtration rate for the risk group was 46.49 ml/min/m². These changes are also reflected by a mean decrease in the serum creatinine of 30.63µmol/L. These results further support the evidence that minimal reductions in the glomerular filtration rate could result in a dramatic increase in mortality ^(8, 43).

Of the 29 children with AKI that had ultrasound done, only 2 had abnormal echopattern and echogenicity, and one of these also had enlarged kidneys. None had shrunken kidneys, that are characteristic of chronic kidney disease, which is a strong risk factor for AKI. Lack of prior

medical history concerning kidney disease was a limitation in determining the risk of AKI among children with pre-existing renal disease, as well as restricted access to the radiology department for ultrasound scan of the AKI group clients during the study period.

5.4 Strength of this Study

This is the first descriptive documentation on the prevalence of acute kidney injury using the modified RIFLE criteria among children with severe malaria in Mulago.

The use of estimated creatinine clearance as a marker of kidney function, as opposed to the use of serum creatinine alone.

The use of serial measurements of serum creatinine to detect AKI that may develop in the course of hospitalization.

5.5 Study Limitations.

Lack of pre-referral treatment documentation concerning intravenous fluids, nephrotoxins like non steroidal anti-inflammatory drugs, gentamycin which could have changed the initial presentation.

The estimation of a normal baseline GFR for age was used in this study, since all patients did not have a prior GFR recorded.

The exclusion of urine output measurement as a measure of AKI. Reduced urine may occur initially, while creatinine is secreted by the kidney, delaying the rise in serum creatinine in the presence of oliguria, thus overestimating the glomerular filtration rate.

Diet, as a major factor influencing serum creatinine was not considered in this study.

The use of one radiographer to report on the status of the kidneys.

Having recruited children after verbal consent could have resulted in selection bias.

CHAPTER SIX

6.0 Conclusion And Recommendations

6.1 Conclusion

The prevalence of acute kidney injury among children with severe malaria admitted in Mulago was at 19.9%, which is very high.

One in five children with severe malaria has AKI.

A child with severe malaria having more severe forms of acute kidney injury is likely to still have acute kidney injury by day seven of admission.

The patients with cerebral malaria and shock is very likely to have acute kidney injury.

6.2 Recommendations

The pRIFLE criteria can be used in the management of children with AKI and severe malaria by careful administration of IV fluids and electrolytes, and close monitoring, since the less severe forms respond adequately to conservative therapy while more severe forms might need renal replacement therapy.

A similar study considering urine output criteria together with serum creatinine is recommended to improve on the sensitivity of the pRIFLE criteria.

A follow up study beyond seven days is useful in determining the mortality associated with acute kidney injury.

Another study with a large sample size is necessary to test for associated factors.

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APPENDIX I

Consent Form

Study Title: Prevalence, severity and immediate of acute kidney injury among children with severe malaria at Mulago Hospital.

Introduction:

I am (representing) Dr. Akobye Winnie from the Department of Paediatrics and Child Health, Makerere University College of Health Sciences, P.O.Box, 7072, Kampala.

Telephone number 0774529916, email grakobye@yahoo.com

I am carrying out a study to investigate the presence of acute kidney injury (AKI) in a child who has malaria infection, since this is one of the complications of malaria. You are being requested to allow your child to participate in this study.

Kidney injury is associated with a high mortality in children with malaria. If identified early, it may be reversed once intravenous fluids are given, and drugs toxic to the kidneys are avoided. In Mulago, the severity of acute kidney injury in children with severe malaria is not known, as well as the clinical presentation and outcome. By allowing your child to participate in this study, you will be helping us to find answers to the above questions.

Study procedure:

On giving consent, you will be asked some questions about your child and a physical examination will be performed. Blood will be drawn for some investigations. The child will receive the standard care according to the Paediatric's department protocols. The results will be given to you, and will help in the management of your child.

Risks:

Some pain as the blood samples are being drawn will be felt, but this has no long term side effects.

Confidentiality:

The names of the child will not appear on the study documents or sample bottles. The results shall not be revealed to any one without your permission.

Rights:

Your child’s participation in this study is completely on voluntary basis. You are therefore free to withdraw from the study at any point in time. Withdraw from the study will not affect management of your child. For any further questions related to the study, please contact me on,

Mobile number: 0774529916, E- Mail address: grakobye@gmail.com

Or contact my supervisors, Dr. Peter Lwabi or Dr. Jane Achan 0713410183.

For any ethical issues concerning this study, please contact the chairman of the Faculty of Medicine Research and Ethics Committee, Makerere Medical School on telephone number: 0414-530-020, or the chairman Professor James Tumwiine on 0772494120.

Consent statement:

I have been informed about the study on acute kidney injury in children with severe malaria at Mulago Hospital. I have been given the explanation of the study procedure, the tests to be carried out, and the risks to my child. I have been assured of confidentiality and that my participation is voluntary.

I hereby give my informed consent for my child to participate in this study.

Name of parent/ guardianSignature/ thumb print

Date/...../.....

Name of investigator signature

date/...../.....

Consent Form- Luganda Version

foomu eraga okukkiriza

Omutwe gw'omusomo: Abaana bameka abalina omusujja gw'ensiri ogw'amaanyi, abafuna obukosefu ku nsigo, amaanyi g'okukosebwa okwo n'ebyo ebiva mu kukosebwa okwo, mu ddwaliro lye Mulago.

Ennyanjula

Nze(akiikirira) Dr. Akobye Winnie okuva mu kitongole ekikola ku ndwadde n'embeera z'abaana mu Ttendekero ly'ebyobulamu mu Yunivasite ye Makerere, Akasanduuke ka posita 7072 Kampala. Ennamba yange ey'essimu 0774529916, endagiriro yange eya yintaneti grakobye@yahoo.com.

Nnoonoyereza ku bukosefu ku nsigo mu baana abalina omusujja gw'ensiri kubanga buno bwe bumu ku buzibu obuva ku bulwadde bw'omusujja. Osabibwa okukkiriza omwaana wo okweetaba mu kunoonyereza kuno.

Obukosefu ku nsigo bwe bumu ku biviraako abaana abalina omusujja gw'ensiri okufa. Bwe buzuulibwa amangu busobola okukyusibwa eccupa z'amazzi ,era n'eddagala ely'obulabe eri ensigo bweriba liyimiriziddwa. Amaanyi g'obukosefu bw'ensigo buno mu baana abalina omusujja gw'ensiri tegamanyiddwa, n'engeri gye bukwaatamu n'ebibuvaamu tebimanyiddwa. Okukkiriza omwaana wo okweetaba mu kunoonyereza kuno, ojja kuba otuyamba okuddamu ebibuuzo ebyo waggulu.

Emitendera okunoonyereza mwe kunaayita

Ng'okkirizza okweetaba mu kunoonyereza, ojja kubuuzibwa ebibuuzo ebikwaata ku mwaana wo era ajja kwekebejjebwa mbagirawo. Ajja kugyibwaako omusaayi okuyamba mu kunoonyereza kuno. Era ajja kufuna obujjanjabi okusenziira ku nzinjajaba y'abaana mu kitongole ekikola ku ndwadde z'abaana. Ebinaava mu musaayi bijja kukubuliirwa era bijja kuyamba ku nzijanjabwa y'omwaana wo.

Obulabe obuyinza okubaawo

Omwaana wo ayinza okuwulira obulumi obutonotono ng'omusaayi gujjibwaako, naye ssi bwankalakkalira.

Okukuuma ebyaama

Amannya g'omwaana wo tegajja kulabika ku biwandiiko byonna eby'okunoonyereza kuno newankubadde ku bucupa bw'omusaayi. Ebinaavaamu tebijja kulagibwaako muntu yenna nga totuwadde lukusa.

Eddembe lyo

Okweetaba kw'omwaana wo mu kunoonyereza kuno kwa kyeyagalire. Oli wa ddembe okukuvaamu ekiseera kyonna. Kino tekikyusa ngeri mwaana wo gyalina kujjanjabibwaamu. Ng'olina ebibuuzo byonna ku kunoonyereza kuno, nkubiraako ku nnamba y'essimu 0774529916, endagiriro ya yintaneti grakobye@gmail.com , oba kubira bakama bange bano wammanga: Dr. Lwabi Peter, oba Dr. Achan Jane 0713410183.

Ng'olina ensonga yonna eyekuusa ku mpisa mu kunoonyereza kuno, yogereganyaamu n'akwaasa empisa mu kunoonyereza mu Ssomero ly'ebyobusawo Mu ttendekero ly'ebyobulamu mu Yunivasite ye Makerere ku ssimu nnamba 0414530020.

Okukkiriza kwange

Ntegezeddwa ku bikwaata ku kunoonyereza ku bukosefu bwensigo mu baana abalina obulwadde bw'omusujja gw'ensiri ogw'amaanyi mu ddwaliro lye Mulago. Nfunye okunyonnyolwa ku ngeri okunoonyereza gye kunaakolebwaamu, emisaayi eginaakebelebwa, n'obulabe obuyinza okubeera ku mwaana wange. Ntegezeddwa ku nkuuma y'ebyaama , nti era okweetabamu kwange kwa kyeyagalire.

Kakaano nzikirizza omwaana wange okweetaba mu kunoonyereza kuno.

Amannya g'omuzadde/alabirira omwaana Omukono gwe/ekinkumu Ennaku z'omweezi

.....

Amannya g'anoonyereza Omukono gwe Ennaku z'omweezi

.....

Assent Form English Version

Study title: Prevalence, severity and immediate of acute kidney injury among children with severe malaria at Mulago Hospital.

Introduction:

I am (representing) Dr. Akobye Winnie from the Department of Paediatrics and Child Health, Makerere University College of Health Sciences, P.O.Box, 7072, Kampala.

Telephone number 0774529916, email grakobye@yahoo.com

I am carrying out a study to investigate the presence of acute kidney injury (AKI) in a child who has malaria infection, since this is one of the complications of malaria. You are being requested to allow to participate in this study.

Kidney injury is associated with a high mortality in children with malaria. If identified early, it may be reversed once intravenous fluids are given, and drugs toxic to the kidneys are avoided. In Mulago, the severity of acute kidney injury in children with severe malaria is not known, as well as the clinical presentation and outcome. By participating in this study, you will be helping us to find answers to the above questions.

Study procedure:

On giving assent, you will be asked some questions and a physical examination will be performed. Blood will be drawn for some investigations. You will receive the standard care according to the Paediatric's department protocols. The results will be given to you, and will help in your management.

Risks:

Some pain as the blood samples are being drawn will be felt, but this has no long term side effects.

Confidentiality:

Your names will not appear on the study documents or sample bottles. The results shall not be revealed to any one without your permission.

Rights:

Your participation in this study is completely on voluntary basis. You are therefore free to withdraw from the study at any point in time. Withdraw from the study will not affect your management. For any further questions related to the study, please contact me on,

Mobile number: 0774529916, E- Mail address: grakobye@gmail.com

Or contact my supervisors, Dr. Peter Lwabi or Dr. Jane Achan 0713410183.

For any ethical issues concerning this study, please contact the chairman of the Faculty of Medicine Research and Ethics Committee, Makerere Medical School on telephone number: 0414-530-020, the chairman Professor James Tumwiine 0772494120.

Assent statement:

I have been informed about the study on acute kidney injury in children with severe malaria at Mulago Hospital. I have been given the explanation of the study procedure, the tests to be carried out, and the risks involved. I have been assured of confidentiality and that my participation is voluntary.

I hereby give my assent to participate in this study.

Name of child	signature/thumb print	Date
.....
Name of witness	signature	Date
.....
Name of investigator	signature	date
.....

Assent Form- Luganda Version

Foomu Eraga Okukkiriza

Omutwe gw'omusomo: Abaana bameka abalina omusujja gw'ensiri ogw'amaanyi, abafuna obukosefu ku nsigo, amaanyi g'okukosebwa okwo n'ebyo ebiva mu kukosebwa okwo, mu ddwaliro lye Mulago.

Ennyanjula

Nze(akiikirira) Dr. Akobye Winnie okuva mu kitongole ekikola ku ndwadde n'embeera z'abaana mu Ttendekero ly'ebyobulamu mu Yuniasite ye Makerere, Akasanduke ka posita 7072 Kampala. Ennamba yange ey'essimu 0774529916, endagiriro yange eya yintaneti grakobye@yahoo.com.

Nnoonyereza ku bokosefu ku nsigo mu baana abalina omusujja gw'ensiri kubanga buno bwe bumu ku buzibu obuva ku bulwadde bw'omusujja. Osabibwa okukkiriza okweetaba mu kunoonyereza kuno.

Obukosefu ku nsigo bwe bumu ku biviraako abaana abalina omusujja gw'ensiri okufa. Bwe buzuulibwa amangu busobola okukyuusibwa eccupa z'amazzi ,era n'eddagala ely'obulabe eri ensigo bweriba liyimiriziddwa. Amaanyi g'obukosefu bw'ensigo buno mu baana abalina omusujja gw'ensiri tegamanyiddwa, n'engeri gye bukwaatamu n'ebibuvaamu tebimanyiddwa. Okukkiriza okweetaba mu kunoonyereza kuno ojja kuba otuyamba okuddamu ebibuuzo ebyo waggulu.

Emitendera okunoonyereza mwe kunaayita

Ng'okkirizza okweetaba mu kunoonyereza, ojja kubuzibwa ebibuuzo ebikukwaatako era ojja kwekebejjebwa mbagirawo. ojja kugyibwaako omusaayi okuyamba mu kunoonyereza kuno. Era

ojja kufuna obujjanjabi okusenziira ku nzinjajaba y'abaana mu kitongole ekikola ku ndwadde z'abaana. Ebinaava mu musaayi bijja kukubuliirwa era bijja kuyamba ku nzijanjabwa yo.

Obulabe obuyinza okubaawo

Oyinza okuwulira obulumi obutonotono ng'omusaayi gujjibwaako naye ssi bwankalakkalira.

Okukuuma ebyaama

Amannya go tegajja kulabika ku biwandiiko byonna eby'okunoonyereza kuno newankubadde ku bucupa bw'omusaayi. Ebinaavaamu tebijja kulagibwaako muntu yenna nga totuwadde lukusa.

Eddembe lyo

Okweetabaakwo mu kunoonyereza kuno kwa kyeyagalire. Oli wa ddembe okukuvaamu ekiseera kyonna. Kino tekikyusa ngeri gy'olina kujjanjabibwaamu. Ng'olina ebibuuzo byonna ku kunoonyereza kuno, nkubiraako ku nnamba ye ssimu 0774529916, endagiririro ya yintaneti grakobye@gmail.com oba kubira bakama bange bano wa mmanga, Dr. Lwabi Peter

....., Oba Dr. Achan Jane 0713410183.

Ng'olina ensonga yonna eyekuusa ku mpisa mu kunoonyereza kuno, yogereganyaamu n'akwaasa empisa mu kunoonyereza mu Ssomero ly'ebyobusawo Mu ttendekero ly'ebyobulamu Mu Yunivasite ye Makerere ku ssimu nnamba 0414530020.

Okukkiriza kwange

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Kakaano nzikirizza okweetaba mu kunoonyereza kuno.

Amannya g'omwaana Omukono gwe/ekinkumu Ennaku z'omweezi

.....

Amannya g'omujulizi Omukono gwe Ennaku z'omweezi

.....

Amannya g'anoonyereza Omukono gwe Ennaku z'omweezi

.....

APPENDIX II:

Questionnaire

1. Identification

a. Study number Study code:

b. IP number.....

c. Date of enrolment.....

2. Social Demographics

a. AGE (months)

b. SEX 1.M..... 2 F.....

C.N.O.K

d. N.O.K occupation.....

-Home address.....

-District -LCI

Referral status;.....

Telephone contacts 1.....

2. Presenting complaints:

1. Fever [] yes [] No. Convulsions [] yes [] no. Repeated convulsions [] yes [] no. Altered mentation [] yes [] no.

2. Cough [] yes [] No .Fast breathing[] yes [] no. Grunting[] yes [] no.

3. Passing tea coloured urine [] yes [] no. Urine amount reduced[] yes [] no

4. Able to drink [] yes [] no. Vomiting [] yes [] no. Diarrhoea [] yes [] no.

Yellow discolouration of eyes [] yes [] No. Flank pain [] yes [] no.

5. Bleeding [] yes [] no.

6. Duration of fever days [] less than a week, [] more than a week.

3. Past medical history;

Intravenous fluid given for current illness [] yes [] no

NSAIDs given [] yes [] no. Gentamycin given [] yes [] no.

3. Physical examination.

A) General examination:

Weight (kg)..... Height (cm)..... Weight/height z score..... MUAC
(cm).....

HC(cm)..... Axillary temperature (°C)..... BP (mmHg) Pulse
Rate/min..... respiratory rate..... Capillary refill..... SpO2.....

Dehydration: No [] Some [] Severe []

Palor: No [] mild [] moderate [] severe []

Jaundice. No [] mild [] moderate [] deep []

Oedema: no [] grade 1 [] grade 2 [] grade 3 []

B) Examination of systems

CVS; bounding pulse [] yes [] no. Third heart sound [] yes [] no.

Cardiac murmur [] yes [] no.

Respiratory; crackles [] yes [] no.

Abdominal exam; hepatomegally [] yes [] no. If yes, centimeters below costal margin=

Tender hepatomegally yes [] no []

Splenomegally [] yes [] no. If yes, centimeters below costal margin=

Tender renal angles [] yes no [].

CNS; Blantyre coma scale=

Focal neurological deficit [] yes [] no

4. Laboratory findings.

CBC

Hb g/dl

RBC (total).....WBC (total)..... leucocyte count.....

HCT (%) MCHC (g/dl)

MCV (pg) RDW

Liver function tests

Total serum bilirubin-----

Direct serum bilirubin-----

Lactate dehydrogenase-----

AST-----

ALT-----

Renal function tests;

Serum creatinine-----Serum urea-----K⁺-----Na⁺-----Cl⁻-----

5.Diagnosis of severe malaria made-----

Follow up date.....2 TO 12 HOURS SINCE ADMISSION

A) General examination:

Weight (kg)..... Height (cm).....Weight/height z score.....MUAC

(cm).....

HC(cm)..... Axillary temperature (°C)..... BP (mmHg)

Pulse Rate/min..... respiratory rate..... Capillary refill.....SpO2.....

Dehydration: No [] Some [] Severe []

Palor: No [] mild [] moderate [] severe []

Jaundice. No [] mild [] moderate [] deep []

Oedema: no [] grade 1 [] grade 2 [] grade 3 []

B)Examination of systems

CVS; bounding pulse []yes []no. Third heart sound []yes []no.

Cardiac murmur []yes []no.

Respiratory; crackles []yes []no.

Abdominal exam; hepatomegally []yes []no. If yes, centimeters below costal margin=

Tender hepatomegally yes [] no []

Splenomegally []yes []no. If yes, centimeters below costal margin=

Tender renal angles []yes []no [].

CNS; Blantyre coma scale=

Focal neurological deficit [] yes []no

FOLLOW UP DATE.....1ST DAY SINCE ADMISSION

A) General examination:

Weight (kg)..... Height (cm).....Weight/height z score.....MUAC

(cm).....

HC(cm)..... Axillary temperature (°C)..... BP (mmHg)

Pulse Rate/min..... respiratory rate..... Capillary refill.....SpO2.....

Dehydration: No [] Some [] Severe []

Palor: No [] mild [] moderate [] severe []

Jaundice. No [] mild [] moderate [] deep []

Oedema: no [] grade 1 [] grade 2 [] grade 3 []

B)Examination of systems

CVS; bounding pulse []yes []no. Third heart sound []yes []no.

Cardiac murmur []yes []no.

Respiratory; crackles []yes []no.

Abdominal exam; hepatomegally []yes []no. If yes, centimeters below costal margin=

Tender hepatomegally yes [] no []

Splnomeagally []yes []no. If yes, centimeters below costal margin=

Tender renal angles []yes no [].

CNS; Blantyre coma scale=

Focal neurological deficiet [] yes []no

Serum creatinine-----

AKI severity-----

FOLLOW UP DATE-----2ND DAY SINCE ADMISSION

A) General examination:

Weight (kg)..... Height (cm).....Weight/height z score.....MUAC

(cm).....

HC(cm)..... Axillary temperature (°C)..... BP (mmHg) Pulse

Rate/min..... respiratory rate..... Capillary refill.....SpO2.....

Dehydration: No [] Some [] Severe []

Palor: No [] mild [] moderate [] severe []

Jaundice. No [] mild [] moderate [] deep []

Oedema: no [] grade 1 [] grade 2 [] grade 3 []

B)Examination of systems

CVS; bounding pulse []yes []no. Third heart sound []yes []no.

Cardiac murmur []yes []no.

Respiratory; crackles []yes []no.

Abdominal exam; hepatomegally []yes []no. If yes, centimeters below costal margin=

Tender hepatomegally yes [] no []

Splenomegally []yes []no. If yes, centimeters below costal margin=

Tender renal angles []yes []no [].

CNS; Blantyre coma scale=

Focal neurological deficit [] yes []no

FOLLOW UP DATE.....3RD DAY SINCE ADMISSION

A) General examination:

Weight (kg)..... Height (cm).....Weight/height z score.....MUAC
(cm).....

HC(cm)..... Axillary temperature (°C)..... BP (mmHg) Pulse
Rate/min..... respiratory rate..... Capillary refill.....SpO2.....

Dehydration: No [] Some [] Severe []

Palor: No [] mild [] moderate [] severe []

Jaundice. No [] mild [] moderate [] deep []

Oedema: no [] grade 1 [] grade 2 [] grade 3 []

B)Examination of systems

CVS; bounding pulse []yes []no. Third heart sound []yes []no.

Cardiac murmur[]yes []no.

Respiratory; crackles []yes []no.

Abdominal exam; hepatomegally []yes []no. If yes, centimeters below costal margin=

Tender hepatomegally yes[] no[]

Splenomegally[]yes []no. If yes, centimeters below costal margin=

Tender renal angles []yes no[].

CNS; Blantyre coma scale=

Focal neurological deficiet [] yes []no

FOLLOW UP DATE----- 4TH DAY SINCE ADMISSION

A) General examination:

Weight (kg)..... Height (cm).....Weight/height z score.....MUAC
(cm).....

HC(cm)..... Axillary temperature (°C)..... BP (mmHg) Pulse
Rate/min..... respiratory rate..... Capillary refill.....SpO2.....

Dehydration: No [] Some [] Severe []

Palor: No [] mild [] moderate [] severe[]

Jaundice. No[] mild[] moderate[] deep[]

Oedema: no [] grade 1 [] grade 2 [] grade 3 []

B)Examination of systems

CVS; bounding pulse []yes []no. Third heart sound []yes []no.

Cardiac murmur[]yes []no.

Respiratory; crackles []yes []no.

Abdominal exam; hepatomegally []yes []no. If yes, centimeters below costal margin=

Tender hepatomegally yes[] no[]

Splnomeagally[]yes []no. If yes, centimeters below costal margin=

Tender renal angles []yes no[].

CNS; Blantyre coma scale=

Focal neurological deficiet [] yes []no

Serum creatinine-----

AKI severity-----

FOLLOW UP DATE----- 5TH DAY SINCE ADMISSION

A) General examination:

Weight (kg)..... Height (cm).....Weight/height z score.....MUAC
(cm).....

HC(cm)..... Axillary temperature (°C)..... BP (mmHg) Pulse
Rate/min..... respiratory rate..... Capillary refill.....SpO2.....

Dehydration: No [] Some [] Severe []

Palor: No [] mild [] moderate [] severe[]

Jaundice. No[] mild[] moderate[] deep[]

Oedema: no [] grade 1 [] grade 2 [] grade 3 []

B)Examination of systems

CVS; bounding pulse []yes []no. Third heart sound []yes []no.

Cardiac murmur[]yes []no.

Respiratory; crackles []yes []no.

Abdominal exam; hepatomegally []yes []no. If yes, centimeters below costal margin=

Tender hepatomegally yes[] no[]

Splenomegally[]yes []no. If yes, centimeters below costal margin=

Tender renal angles []yes no[].

CNS; Blantyre coma scale=

Focal neurological deficit [] yes []no

FOLLOW UP DATE-----6TH DAY SINCE ADMISSION

A) General examination:

Weight (kg)..... Height (cm).....Weight/height z score.....MUAC
(cm).....

HC(cm)..... Axillary temperature (°C)..... BP (mmHg) Pulse
Rate/min..... respiratory rate..... Capillary refill.....SpO2.....

Dehydration: No [] Some [] Severe []

Palor: No [] mild [] moderate [] severe[]

Jaundice. No[] mild[] moderate[] deep[]

Oedema: no [] grade 1 [] grade 2 [] grade 3 []

B)Examination of systems

CVS; bounding pulse []yes []no. Third heart sound []yes []no.

Cardiac murmur[]yes []no.

Respiratory; crackles []yes []no.

Abdominal exam; hepatomegally []yes []no. If yes, centimeters below costal margin=

Tender hepatomegally yes[] no[]

Splenomegally[]yes []no. If yes, centimeters below costal margin=

Tender renal angles []yes no[].

CNS; Blantyre coma scale=

Focal neurological deficit [] yes []no

FOLLOW UP DATE-----7TH DAY SINCE ADMISSION

A) General examination:

Weight (kg)..... Height (cm).....Weight/height z score.....MUAC
(cm).....

HC(cm)..... Axillary temperature (°C)..... BP (mmHg) Pulse
Rate/min..... respiratory rate..... Capillary refill.....SpO2.....

Dehydration: No [] Some [] Severe []

Palor: No [] mild [] moderate [] severe[]

Jaundice. No[] mild[] moderate[] deep[]

Oedema: no [] grade 1 [] grade 2 [] grade 3 []

B)Examination of systems

CVS; bounding pulse []yes []no. Third heart sound []yes []no.

Cardiac murmur[]yes []no.

Respiratory; crackles []yes []no.

Abdominal exam; hepatomegally []yes []no. If yes, centimeters below costal margin=

Tender hepatomegally yes[] no[]

Splenomegally[]yes []no. If yes, centimeters below costal margin=

Tender renal angles []yes no[].

CNS; Blantyre coma scale=

Focal neurological deficit [] yes []no

Serum creatinine-----

AKI severity-----

APPENDIX III:

WHO Definition Of Severe Malaria.

(From Organization Wh. World Malaria Report. Geneva 2010.)

In a patient with *P. falciparum* asexual parasitaemia and no other obvious cause of symptoms, the presence of one or more of the following clinical or laboratory features classifies the patient as suffering from severe malaria

Clinical features:

- impaired consciousness or unrousable coma
- prostration, i.e. generalized weakness so that the patient is unable walk or sit up without assistance
- failure to feed
- multiple convulsions – more than two episodes in 24 h
- deep breathing, respiratory distress (acidotic breathing)
- circulatory collapse or shock, systolic blood pressure < 70 mm Hg in adults and < 50 mm Hg in children
- clinical jaundice plus evidence of other vital organ dysfunction
- haemoglobinuria
- abnormal spontaneous bleeding
- pulmonary oedema (radiological)

Laboratory findings:

- hypoglycaemia (blood glucose < 2.2 mmol/l or < 40 mg/dl)
- metabolic acidosis (plasma bicarbonate < 15 mmol/l)
- severe normocytic anaemia (Hb < 5 g/dl, packed cell volume < 15%)
- haemoglobinuria
- hyperparasitaemia (> 2%/100 000/μl in low intensity transmission areas or > 5% or 250 000/μl in areas of high stable malaria transmission intensity)
- hyperlactataemia (lactate > 5 mmol/l)
 - renal impairment (serum creatinine > 265 μmol/l).

APPENDIX IV:

Assessment Of The Level Of Consciousness

Blantyre Coma Scale (From Molyneux, ME, Taylor, TE, Wirima, JJ, Borgstein, A. Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children. Q J Med 1989; 71:441).

Eye movement

Watches or follows ----- 1

Fails to watch or follow----- 0

Best motor response

Localizes painful stimulus----- 2

Withdraws limb from painful stimulus-----1

No response or inappropriate response----- 0

Best verbal response

Cries appropriately with pain, or, if verbal, speaks 2

Moan or abnormal cry with pain----- 1

No vocal response to pain----- 0

Total -----

APPENDIX V

Blood Pressure Charts

Blood Pressure Levels for Boys by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg)							Diastolic BP (mmHg)						
		← Percentile of Height →							← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90

Blood Pressure Levels for Boys by Age and Height Percentile (Continued)

Age (Year)	BP Percentile ↓	Systolic BP (mmHg)							Diastolic BP (mmHg)						
		← Percentile of Height →							← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

Blood Pressure Levels for Girls by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg)							Diastolic BP (mmHg)						
		← Percentile of Height →							← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88

Blood Pressure Levels for Girls by Age and Height Percentile (Continued)

Age (Year)	BP Percentile ↓	Systolic BP (mmHg)							Diastolic BP (mmHg)						
		← Percentile of Height →							← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

APPENDIX VI

Volume Depletion In Infants And Children

Findings	No dehydration	Some dehydration	Severe dehydration
Pulse	Full, normal rate	Rapid	Rapid and weak
Systolic pressure	Normal	Normal or low	Low
Respiration	Normal	Deep, rate may be increased	Deep, tachypnea
Buccal mucosa	Tacky or slightly dry	Dry	Parched
Anterior fontanelle	Normal	Sunken	Markedly sunken
Eyes	Normal	Sunken	Markedly sunken
Skin turgor	Normal	Reduced	Tenting
Skin	Normal	Cool	Cool, mottled, acrocyanosis
Urine output	Normal or mildly reduced	Markedly reduced	Anuria
Systemic signs	Increased thirst	Listlessness, irritability	Grunting, lethargy, coma

APPENDIX VII:

Normal Glomerular Filtration Rate For Children.

(**From National** Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease. Evaluation, classification and stratification. Am J Kidney Dis 2002;39(Suppl 1):S1-S266. Table 24 (page S56)

Age, gender	Schwartz formula	Mean eCCl +/- SD ml/min/1.73m ²
>8 weeks(male and female)	eCCl= 0.45*(length/SCr)	95.7+/- 21.7
2-12 years(male and female)	eCCl= 0.55*(length/SCr)	133.0 +/- 27

Schwartz Formula

$$eCCl = K \times \frac{L}{S_{cr}}$$

eCCl is estimated creatinine clearance in milliliters per minute per 1.73m²

L is height in centimeters

Scr is serum creatinine in milligrams per deciliter

K is a constant; 0.45 for children less than 2 years

0.55 for children 2 years to 12 years

APPENDIX VIII:

Management Aki(Kdigo Clinical Practice Guidelines For Acute Kidney Injury, 2012)

Fluid Balance;

1. The use of isotonic crystalloids is recommended as the initial management for expansion of intravascular volume in patients with acute kidney injury. For severe dehydration, give 20mls/Kg normal saline over 30 minutes. This may be repeated if there is no initial improvement.
2. For evolemia, maintenance fluid is 300-500ml/m² + GIT losses + urinary losses
3. For hypervolemia; Pedal edema, hypertension and pulmonary edema
Fluid restriction. If the patient is oliguric, high dose frusemide 2-5mg/Kg is given once. Maintain IV frusemide at 0.1mg/Kg/hr if response is good. If there is no urine produced in 2 hours of initial bolus, discontinue frusemide, calculate % fluid overload(=total fluid in – total fluid out X 100). Dialysis if overload is 10-15%.

Admission weight

4. Monitor fluid input, output, body weight and blood pressure.

Electrolyte Balance:

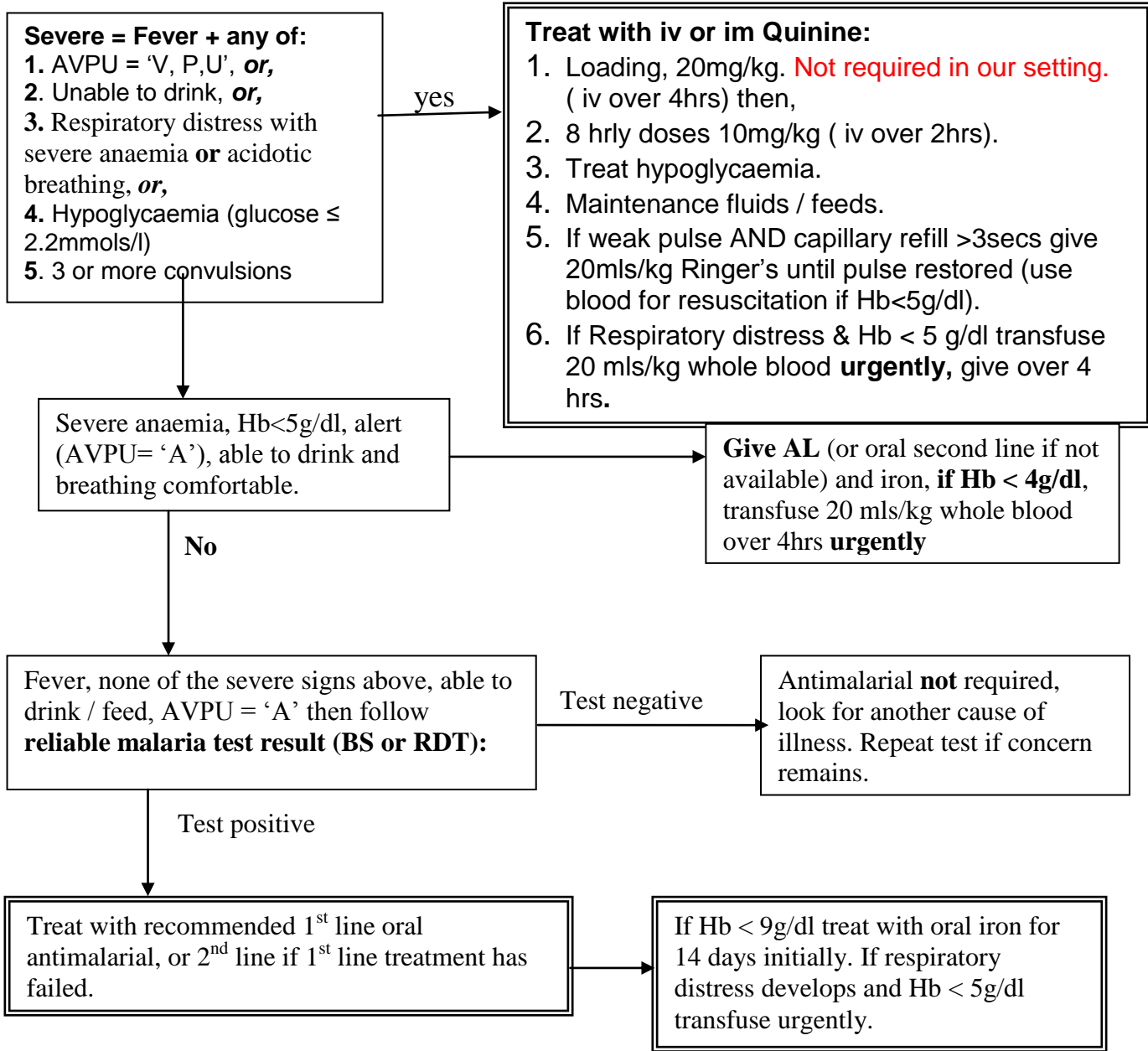
1. Restrict sodium to 2-3mEq/Kg/24hrs
2. Hyperkalemia(if > 6.5mEq/L, or ECG changes) Stabilize cardiac membrane with Ca gluconate 1mg/kg. Push K⁺ back into cell with salbutamol nebulized 2.5mg/kg, IV glucose 1g + 0.1U/kg, or Na bicarbonate 1mEq/Kg o'er 30 min. Move K⁺ out of the body with kayexalate 1gm/kg.
3. Hyperphosphatemia is treated with phosphate binders, calcium carbonate 45mg/Kg/day in 4 divided doses.

4. Hypocalcemia is treated with calcium carbonate 45mg/kg/day in 4 divided doses.

Others

1. The recommendation is to use enteral feeding, not restricting proteins, maintaining total energy intake of 20-30Kcal/Kg/day.
2. Avoidance of aminoglycosides in children with impaired renal functioning. For those with normal kidney function, aminoglycosides are given as single dose.
3. Use emergent renal replacement therapy urgently in these situations; life threatening hyperkalemia, acidemia, in pulmonary edema, and in uremia (pericarditis, bleeding, neuropathy).
4. Nonemergent indications for renal replacement therapy include fluid overload and solute control.
5. Monitor serum creatinine and urine output.

APPENDIX IX: Severe malaria protocol; department of paediatrics and child health, 2012



Treatment failure:

Consider other causes of illness / co-morbidity

A child on oral antimalarials who develops signs of severe malaria (Unable to sit or drink, AVPU=U or P and / or respiratory distress) at any stage should be changed to iv quinine.

If a child on oral antimalarials has fever **and a positive blood slide** after 3 days (72 hours) then check compliance with therapy and if treatment failure proceed to second line treatment