INCIDENCE AND RISK FACTORS FOR NEPHROTOXICITY ASSOCIATED WITH AMINOGLYCOSIDE THERAPY AMONG HOSPITILIZED CHILDREN AT KENYATTA NATIONAL HOSPITAL, KENYA.

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Title of the work: Incidence and risk factors of nephrotoxicity associated with aminoglycoside therapy among hospitalized children at Kenyatta National hospital, Kenya.

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DEDICATION

I dedicate this work to my mother for the constant support and encouragement. I would also like to appreciate my sons Andrew and Oliver for their patience and support.

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LIST OF ABBREVIATIONS

AKI	Acute Kidney Injury
ALP	Alkaline phosphatase
APGAR	Appearance, Pulse, Grimace, Activity and Respiration
GFR	Glomerular filtration rate
H/ hrs.	Hours
KIDGO	Kidney Disease Improving Global Outcomes
Kg	Kilo grams
KNH	Kenyatta National Hospital
Mg	Milligrams
NAG	N acetyl D-Glusaminodase
NSAIDs	Non-Steroidal Anti Inflammatory Drugs
PDA	Patent Ductus Arteriosus
RCT	Randomized Control trial
Scr	Serum creatinine
UoN	University of Nairobi
WHO	World Health Organization

DEFINITION OF OPERATIONAL TERMS.

Acute Kidney Injury.

In this study, it is defined by the RIFLE criteria as rise in serum creatinine by 2 to 3 times the reference serum creatinine levels.

APGAR score.

A simple and repeatable assessment of the health of a newborn at 1, 5, and 10 minutes after birth. It is determined by evaluating the newborn baby on five simple criteria on a scale from zero to two, based on the five characteristics of color, heart rate, response to stimulation of the foot sole, muscle tone and respiration with 10 being the perfect score. The five criteria are summarized using words chosen to form an acronym (Appearance, Pulse, Grimace, Activity, and Respiration).

Low birth-weight neonates.

Refers to the newborn babies weighing <2500gms at birth.

Neonates.

Refers to the newborn babies, either preterm or terms of age ≤28 days.

Normal birth-weight neonates.

Refers to a weight of ≥ 2500- 4500gms at birth.

Nephrotoxicity.

In this study, nephrotoxicity will refer to kidney injury associated with aminoglycoside use, and classified as mild, acute kidney injury or kidney failure according to the RIFLE criteria of kidney injury.

Children.

In this study it will refer to the children aged 2 to 5 years and below who were recruited to this study.

Perinatal asphyxia.

A medical condition resulting from deprivation of oxygen to a newborn infant that lasts long enough during the birth process to cause physical harm. Hypoxic damage can occur to most of the infant's organs. Usually the brain is the most affected and the damage may

manifest as either mental, such as developmental delay or intellectual disability, or physical, such as spasticity.

Pre term neonates.

These are newborn babies born at a gestational age of < 37 weeks.

Term neonates.

These are newborn babies born at gestational age of ≥ 37- 42 weeks.

Very low birth weight neonates.

These are neonates refers to a weight of < 1500gms at birth.

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ABSTRACT.

Background.

Aminoglycoside antibiotics are routinely used in neonates for treatment of neonatal sepsis, meningitis and burns in synergy with beta lactam antibiotics and in older children for treatment of acute respiratory tract infections, intra-abdominal infections and complicated urinary infections. They are effective against a wide range of Gram-positive and Gram-negative bacteria like Staphylococcus and Enterococcus, in synergy with β-lactam antibiotics. However, they have a narrow therapeutic window and are nephrotoxic. The risk of nephrotoxicity is increased by other factors such as age, birth weight, other illnesses, and concurrent use of nephrotoxic medications among others.

Main objective

To determine the incidence and risk factors of nephrotoxicity associated with aminoglycosides use among children aged 5 years and below admitted at (KNH), and describe the short term outcomes of therapy.

Methodology

This was a hospital based prospective cohort study that targeted all children, age five years and below, who were treated with aminoglycosides for the period of July 2018 to September 2018. The study was conducted at the Kenyatta National Hospital general pediatric wards, and the newborn unit. They were recruited consecutively until a sample size of 195 was reached. Their baseline urea, electrolyte and serum creatinine levels were measured before initiating aminoglycoside treatment. Follow up urea, electrolyte and creatinine levels were measured at termination of the aminoglycoside therapy.

Results

Of the 195 (100%) children, 20 (10.25%) developed nephrotoxicity. Of these, 13 (65%) developed nephrotoxicity that was mild and reversible (P=0.001), while 4 (20%) of them developed acute kidney injury and 3(15%) developed kidney failure.

The neonates who constituted 58 (28.7%) of the study population, were 3.54 (95% CI 1.6-8.21) times more likely to develop nephrotoxicity compared to older children (P=0.003). Low birth weight neonates were 4.73 (95% CI: 1.8-12.5) times more likely to develop nephrotoxicity than those who weighed >2500gms at birth (P=0.002).

Neonates with neonatal sepsis were 4.91 (95% CI: 2.07-11.62) times more likely to develop nephrotoxicity than those treated for other conditions (P=0.001). Most patients who developed nephrotoxicity, 13(65%) were switched to cephalosporin antibiotics, while 5 (25%), and continued on aminoglycoside treatment with dose adjustments. Most patients who developed nephrotoxicity were switched to cephalosporin antibiotics and there was no mortality reported during the study period.

Conclusion and recommendations.

Aminoglycosides should be used with caution in high-risk populations like the neonates, especially the low birth-weight, asphyxiated and those suffering from sepsis. Routine monitoring of kidney functions should be considered within 72 hours of initiating aminoglycoside use in all neonates since they are at a higher risk of developing nephrotoxicity. Larger studies need to be conducted to assess for correlation between maternal factors and other patient related risk factors with nephrotoxicity, and to assess the long-term outcomes of the patients who develop aminoglycoside-associated nephrotoxicity.

CHAPTER 1 : INTRODUCTION.

1.1. Background

Aminoglycoside antibiotics are often used among neonates for treatment of neonatal sepsis, pneumonia, meningitis, burns in synergy with beta lactam antibiotics and in older children for treatment of acute respiratory infections, intra-abdominal infections and complicated urinary infections. They act against a wide range of Gram-positive and Gram-negative bacteria like Staphylococcus and Enterococcus, especially in synergy with β-lactam antibiotics. The aminoglycoside antibiotics commonly used in Kenyatta National Hospital (KNH) pediatric department are gentamicin, Amikacin and vancomycin.

Aminoglycosides are widely used because they are affordable, easily available and generally well tolerated. However, aminoglycosides have a narrow therapeutic window and they are nephrotoxic. The nephrotoxicity is often mild and reversible in nature. The reported rates of nephrotoxicity among children according to a World Health Organization (WHO) review in 2008 varied widely from 1.2% up to as high as 55%. (1). A study on neonates who were admitted in an Australian hospital on aminoglycosides, 8% to 26% developed nephrotoxicity, which was mostly mild and reversible (2). Recent epidemiological studies using more widely accepted definitions have reported acute kidney injury in 20 to 33% of children exposed to aminoglycosides (3). A retrospective cross- sectional study done in Kenya , Kenyatta National Hospital on 194 children below the age of 12 years on aminoglycosides, observed that 132 (68%) of them had baseline plasma creatinine measurements taken. Of those with baseline creatinine measurements, 17 (12.9%) had follow up creatinine levels measured. Out of the 17, 1(5.8%) was found to have developed nephrotoxicity with 30% rise in serum creatinine, within 10 days of being on gentamicin (4).

Some factors also predispose pediatric patients to nephrotoxicity, such as age, preterm neonates, low birth weight, neonatal sepsis, birth asphyxia, concurrent use of nephrotoxic medication among others. A study done at a U.S.A centre on 108 preterm neonates documented 86% exposure to gentamicin. Of these 26% developed acute kidney injury (5). There are limited studies done in resource constraint countries on aminoglycoside induced nephrotoxicity.

This study aims to inform policy on management of pediatric patients on aminoglycoside therapy on the need for daily monitoring of kidney functions in this population. This will

enhance early detection of kidney injury and prevent progression to irreversible kidney failure.

1.2. Problem statement.

The incidence of aminoglycoside-associated nephrotoxicity has not been widely studied especially in resource-limited countries. Children, especially those below five years are more predisposed to nephrotoxicity. Other risk factors for nephrotoxicity include the neonatal age, low birth weight, neonatal sepsis, dehydration status, nutrition status, concurrent use of nephrotoxic medication and any underlying illness. A WHO review done in 2008 reported a prevalence of 8-26% of aminoglycoside nephrotoxicity.

As much as nephrotoxicity is a known adverse effect of aminoglycosides, routine monitoring of kidney function and therapeutic drug monitoring is not done routinely. A cross sectional study done in a hospital in South Africa reported that blood levels were performed in only 29.23% of patients using gentamicin prescriptions and 57.89% of patients on amikacin(6). A retrospective baseline study done in a hospital in Kenya (KNH) on 194 children below 12 years, who were on aminoglycosides, found that 132 of the children (68%) had baseline serum creatinine measured. Of those with baseline creatinine measurements, only 17 (12.9%) had follow up creatinine levels measured. The prevalence of nephrotoxicity was 1(5.8%) with 30% rise in serum creatinine, (4). It was established that routine monitoring of urea, electrolyte and serum creatinine was not done consistently. The incidence and short-term outcomes of aminoglycoside-associated nephrotoxicity is in this population is not known.

1.3. Study question.

1. What is the incidence of aminoglycosides associated nephrotoxicity among children aged five years and below admitted in KNH?
2. What are the risk factors influencing aminoglycoside associated nephrotoxicity in this population?
3. What are the short term outcomes of the patients who experienced nephrotoxicity?

1.4. Study objectives

Main objective

To determine the incidence and risk factors of nephrotoxicity associated with aminoglycosides use among children aged 5 years and below admitted at (KNH), and describe the short term outcomes of therapy.

Specific objectives

1. To determine the incidence of nephrotoxicity among children aged five years and below, on aminoglycosides, admitted at KNH.
2. To determine and describe patient and maternal risk factors associated with aminoglycoside associated nephrotoxicity in this population.
3. To describe the short-term outcomes of the participants who experienced nephrotoxicity.

1.5. Study significance

A review done by WHO in 2008, revealed a prevalence of 8-26% of aminoglycoside-associated nephrotoxicity in children (7). In Kenya, the prevalence of aminoglycoside-associated nephrotoxicity has not been studied. This study conducted routine monitoring of the urea, electrolyte and serum creatinine levels and determined the incidence of nephrotoxicity in children aged five years and below, receiving aminoglycosides at KNH. Data were collected and documented on the risk factors associated with nephrotoxicity in this population. Based on the severity and long-term consequences of kidney injury, early detection of nephrotoxicity is important, especially among children on aminoglycosides, as dose adjustment will minimize the risk of progression to irreversible kidney injury. The findings may inform decision making about management of children using aminoglycosides, while taking into consideration the risk factors associated with nephrotoxicity. The findings of this study may also inform policy changes on the need for daily monitoring of kidney functions in the pediatric population on aminoglycoside therapy.

CHAPTER 2 : LITERATURE REVIEW.

2.1. Aminoglycoside toxicity in children

Aminoglycoside antibiotics are bactericidal agents that are active against the gram positive and gram-negative bacteria, including Klebsiella, Pseudomonas, Escherichia Coli and Enterobacter species (2). In infants and older children–aminoglycoside antibiotics are recommended for treatment of acute respiratory infections, intra-abdominal sepsis, and complicated urinary tract infections (7). According to the World Health Organization (WHO) treatment guidelines for neonatal sepsis, aminoglycosides (gentamicin and amikacin) are the first line management drugs in combination with beta lactam antibiotics (2).

Aminoglycosides have a narrow therapeutic window, and the children treated with either Gentamicin or Amikacin are at increased risk of developing nephrotoxicity, loss of hearing, skin rashes, dizziness, and general body weakness. Nephrotoxicity is highest with the use of gentamicin and decreases with tobramycin, amikacin, and netilmicin.(8)

Drug related nephrotoxicity is characterized by a reduction in kidney function, associated with ingestion of a drug, resulting in derangements in fluid balance, electrolytes, and waste products (9). Based on the RIFLE criteria, diagnosis is dependent on a rise in serum creatinine (S Cr) levels by $\geq$ 1.5 times the reference serum creatinine level or decrease in the urine output to <0.5 Ml/kg/h for > 6 hours as a risk of injury, or acute kidney injury of a rise in serum creatinine by $\geq$ 2-3 times , of kidney failure of a rise by $\geq$ more than 3 times the baseline serum creatinine (10).

2.2. Mechanism of nephrotoxicity due to aminoglycosides therapy in children.

Nephrotoxicity associated with aminoglycosides is commonly due to tubular necrosis, which leads to a rise in the serum creatinine levels of greater than or equal to 50%. When an aminoglycoside is filtered across the glomerulus, most of the drug is excreted, with tubular re-absorption of only 5-10 percent (11).

Normally, intracellular accumulation of aminoglycoside antibiotics is confined to the S1 and S2 segments of the proximal tubule but following ischemia, accumulation can occur in the S3 segment. Here they interact with phospholipids on brush membranes and they are inserted into lysosome. Aminoglycosides exert their toxic effect by altering phospholipids metabolism within tubular cells (12). They can also cause obstruction of renal blood flow through vasoconstriction (7).

2.3. Clinical signs and symptoms of nephrotoxicity

Glomerular filtration rate is determined using the serum creatinine levels, which are largely dependent on the amount of muscle mass of a neonate and to a lesser extent on the amount of ingested protein. Immediately after birth to 72 hours, the neonatal serum creatinine level reflects the maternal creatinine levels (13). The serum creatinine levels decreases at varying rates after birth, depending on the gestational age, to reflect normal creatinine production and renal function. The normal range for neonates varies from 17µmol/L to 70 µmol/L.

Neonates and infants have much less muscle mass compared to adults. Therefore serum creatinine levels are lower in the neonates and they increase with age as accretion of muscle mass occurs to reach adult levels (13).

Neonatal or intrauterine renal toxicity may result in an impaired glomerular filtration, tubular function, hormonal production and catabolism. These will present as kidney failure with proteinuria, aminoaciduria, glycosuria and retention of waste products of metabolism (urea and plasma creatinine) (14).

Tubular injury may present with inability to dilute and concentrate the urine, polyuria, inability to eliminate metabolically produced or ingested acids and alkali causing metabolic alkalosis or acidosis, and impaired regulation of electrolyte balance resulting in either low or high blood pressure(15).

The early clinical indicators of tubular injury include: Proteinuria characterized by (albuminuria, globulinuria or 1,2-microglobulinuria) (15), abnormal urine sedimentation characterized by elevated urinary levels of red blood cells, pyuria, casts, and renal tubular epithelial cells, increase in levels of urinary enzymes like alkaline phosphatase, glutamyl trans-peptidase, alanine aminopeptidase, isoenzymes of glutathione transferase, N-acetyl- D – glucosaminidase (NAG)(16). Increased excretion of alkaline phosphatase (ALP), -glutamyl trans-peptidase (GTP), and alanine aminopeptidase enzymes found on the brush border of renal tubular cells may also reflect damage of the brush border membrane, with loss of the microvilli (16). Increase in urinary NAG activity , however, is a reflection of increased lysosomal activity without cellular damage (14).

2.4. Epidemiology of nephrotoxicity in children on aminoglycoside therapy.

According to a review of studies done by WHO in 2008 on nephrotoxicity in children receiving aminoglycosides, a prevalence varying from 2-55% was reported (17). A review done in Australia reported an incidence of 8-26% of nephrotoxicity in neonates treated with

gentamicin for more than seven days. However, the reported nephrotoxicity was mild and reversible (2). In a Cochrane systematic review of nine randomized controlled trials (RCTs) done by the International Child Health Review to establish the rate of nephrotoxicity associated with gentamicin, no nephrotoxicity was reported in six of the RCT's while one reported a clinically insignificant primary nephrotoxicity. Other two RCTs reported 2% and 15% prevalence of nephrotoxicity respectively (18). The risk of nephrotoxicity associated with aminoglycosides in some studies has been shown to be relatively low. However, it is increased when the neonates are exposed to other risk factors, such as asphyxia, very low birth weight, history of use of nephrotoxic agents in the mothers while pregnant and concomitant use of nephrotoxic agents like NSAIDS, cephalosporin, amphotericin B, acyclovir among others. The risk is much lower when the required therapeutic levels are maintained (19). A study done in Houston in 2007, found out that pharmacologic drugs accounted for 16% of kidney injury in children below 12 years old (20).

There were no studies found in other resource limited countries, on aminoglycoside toxicity. However, in a study done in Kenyatta National Hospital, Kenya, 194 children on aminoglycosides were studied retrospectively, it was reported that 68% had baseline plasma creatinine measurements taken. Of those with baseline creatinine measurements, 17 (12.9%) had follow up creatinine levels measured. Out of the 17, 1(5.8%) was found to have developed nephrotoxicity as defined by a 30% rises in serum creatinine. This study also found out that 5% of the children had received gentamicin, while 4.5% others were on amikacin. Routine monitoring of the serum creatinine levels was not done consistently (4)**.**

2.5. Indicators of nephrotoxicity in children on aminoglycoside therapy.

Serum creatinine level is a measure of deterioration in kidney function. It takes approximately 48-72 hours for the serum creatinine levels to rise, after nephrotoxicity has occurred, (21). The incidence of AKI associated with Vancomycin in a prospective study of 418 infants (0-2 years at the Texas children's hospital (ICU) was 7.2%. The AKI was defined as a rise in serum creatinine by more than 2 times from the baseline serum creatinine within 72 hours of using vancomycin (22). In the immediate postnatal period, neonatal serum creatinine level is a reflection of the level of the maternal creatinine and varies depending on the gestational age and weight (14).

2.5.1. Estimated glomerular filtration rate (e-GFR).

The e-GFR is calculated based on serum creatinine levels and can be used for estimating the kidney function in children. In term neonates, the normal GFR ranges between 10-20mL/min/1.73m² and up to the first two weeks of life, it increases to between 30-40mL/min/1.73m². In preterm neonates, the GFR is even lower and it increases more slowly compared to term infants. GFR reaches adult levels by the age of 2 years (23).

2.5.2. Schwartz formula (23);

$$GFR = \frac{k \times \text{body length (cm)}}{\text{Serum creatinine (µmol/L)}}$$

Where, "k", represents a proportionality constant that varies with age as illustrated below, (Table 2.1).

2:1. Proportionality constant (k) for children at different ages (23)

Age group	**K**
Low birth weight infants, age<1year and <1500gms	0.33
Term infants to 1year old	0.45
Children, age 2-12yrs	0.55

2.5.3. Urinary biomarkers.

Urinary biomarkers of acute kidney injury have also been used to detect kidney injury. Several studies have proposed urinary biomarkers to be early indicators of acute kidney injury. The biomarkers that have been studied include Cystatin-C, urine neutrophil gelatinase associated lipocalin and kidney injury molecule-1 among others (16). A prospective study of 108 asphyxiated neonates in Pumwani Maternity Hospital and Kenyatta National Hospital in Kenya, reported that the use of urine neutrophil gelatinase associated lipocalin gave a higher incidence of AKI as compared to serum creatinine. The sensitivity, specificity, positive and negative predictive value and likelihood ratios were 88, 56, 30, 95 %, 2 and 0.2 respectively (24).

A meta-analysis of 11 studies that included both children and adults (sample size 90,500) established that the use of Cystatin-C alone or in combination with serum creatinine, improves the strength of association between e-GFR and the presence of end-stage renal

disease as well as the risk of death (25). However, these biomarkers have not been adopted in KNH and serum creatinine is widely used as the standard measure of kidney function.

Calciuria and magnesuria is an early indicator of aminoglycoside associated kidney injury. Aminoglycoside antibiotics compete with calcium to bind to cells in the renal tubular brush border leading to calciuria with increased calcium levels in urine (26).

2.6. Risk factors associated with aminoglycosides nephrotoxicity.

2.6.1 Patient related factors.

2.6.1.1. Neonatal age

Neonatal age is significantly associated with kidney injury. This is because there kidneys are not fully developed; hence exposing them to nephrotoxicins increases the chances of developing nephrotoxicity.(1,27) The neonates admitted at the hospitals are also exposed to multiple risk factors like underlying illnesses, dehydration among others that may further predispose them to AKI as described in the following sections.

2.6.1.2. Low birth weight.

Preterm babies born at week 23-37 are at higher risk of developing acute kidney failure due to the mere fact that the kidneys are still undergoing nephrogenesis at the time of birth. Very low birth-weight infants (< 1500mg) were at higher risk (79%) of developing AKI (28).

2.6.1.3. Malnourishment and Hydration status.

Malnutrition and volume depletion has been shown to be risk factors of acute kidney injury in children and adults. A study done in India (Udaipur) analyzed 272 dehydrated neonates, 74.3% of them developed acute kidney injury (29). Children with malnourishment have been shown to have a decreased GFR and renal plasma flow (30).

2.6.2. Underlying clinical conditions

2.6.2.1. Low APGAR score and a diagnosis of asphyxia.

Most neonates with poor APGAR scores are admitted to neonatal care units where they undergo various interventions like assisted ventilation, phototherapy, and receive antibiotics for neonatal sepsis which increases their risk for developing kidney injury (31).

Asphyxia is among the leading causes of acute kidney injury in neonates. In a study involving 60 children admitted in KNH with asphyxia, 7 (11.6%) of the neonates developed AKI by day 3, defined as serum creatinine of >133μmol/l. It was determined that AKI is likely to

occur in 1 out of 8 neonates with perinatal asphyxia and 5 out of 7 of the neonates are likely to die by day 4. The mortality rate among neonates with perinatal asphyxia and AKI was found to be 71.4% with a 24 fold higher risk of death, p=0.001{95 CI (3.7-15.7)}. This study did not however determine the proportion of these neonates that received aminoglycosides (32).

2.6.2.2. Neonatal sepsis.

Sepsis is a significant cause of neonatal kidney injury. Acute kidney injury might develop after developing sepsis, or sepsis can occur in children who have acute kidney failure irrespective of other causes. A study involving 611 critically ill infants was done to determine the association between sepsis and AKI in critical care unit. Of these, 174 (28%) who were treated for sepsis developed AKI while undergoing treatment , 243(40%) developed sepsis in a median of 5 days after developing AKI, 194(32%) remained sepsis free (33). It concluded that AKI can occur either before or after developing sepsis, especially in neonates (28).

2.6.3. Drug related factors.

2.6.3.1. Dosing interval and duration of aminoglycoside therapy.

According to the WHO guidelines, it is recommended that aminoglycosides especially gentamicin and amikacin are administered to children every 12 hours. However, pharmacokinetic studies have established that a 24 hourly dosing decreases the risk of aminoglycosides nephrotoxicity in children, as opposed to 12 hourly dosing (34). Treatment duration of more than 7 days increases the risk of nephrotoxicity. This is due to renal tubular accumulation of the drug exerting a direct toxic effect on the kidneys (17). In a retrospective study done in Texas Children Hospital, children below 12 years who were treated with aminoglycosides for more than five days were observed and 33% of them developed nephrotoxicity as defined by the RIFLE criteria (35).

A randomized control trial conducted in a district hospital in Kenya followed 292 infants aged >7 days old. Of these, 136 (46.7%) were treated with a once daily dosing of gentamicin while 123 (53.4%) were treated with multiple daily dosing of gentamicin respectively. Mortality rate was similar in both groups and clinically insignificant. Renal toxicity was observed in less than 2% of the infants. Once daily dosing was found to be as effective as twice daily dosing and less costly to the hospital (36).

2.6.3.2. History of using NSAIDS and other nephrotoxic drugs

A cohort study of 594 term neonates diagnosed with Patent ductus arteriosus (PDA) and treated with NSAIDS and aminoglycosides reported an incidence of AKI of 11.9% , of whom 44(14.8%) had received NSAIDS and aminoglycosides while 27(9.1%) received only aminoglycosides. The attributable risk of NSAIDS was reported at 5.7% (95% CI, 0.5, 11.0), (37). A similar study on neonates with PDA and receiving gentamicin, reported that NSAID therapy increased the risk of AKI by about 6% (27).

In a case control study done to determine the risk factors associated with acute kidney failure in preterm neonates, the mothers characteristics increased the odds of developing AKI as follows; those who had used antibiotics during pregnancy had 2.29(95% CI~1.04,5.07), NSAIDS 2.35(95% CI~1.67,4.7 and using drugs during delivery 2.37(95% CI~1.13,5.04.(19). The nephrotoxicity associated with aminoglycosides is highest with gentamicin, followed with tobramycin, amikacin and netilmicin in that order (12). Other agents that have been found to increase the risk of acute kidney failure in children include; diuretics like furosemide, amphotericin B, the β-lactam antibiotics and related agents. The potential of β-lactam antibiotics to cause nephrotoxicity decreases in the order of: carbapanems> cephalosporins> penicillins> monobactams. However the third generation cephalosporins are well tolerated by the kidney (9).

2.7. Management of drug induced nephrotoxicity.

The best approach to manage drug induced nephrotoxicity is by withdrawing the implicated medicine before medical management. Nephrotoxicity induced by aminoglycosides is mostly reversible or transient (38). However, if nephrotoxicity persists even after withdrawal of aminoglycosides, the usual management protocol of acute kidney injury should be followed. The clinician must support cardio-respiratory system, maintain maximum nutrition, balance homeostasis and manage the consequences of nephrotoxicity. Dialysis can be used to provide renal support to enable achievement of the goal oriented therapies (39). Dopamine can be used to increase renal perfusion (40). Use of indomethacin instead of ibuprofen in neonates treated for PDA is encouraged since it has been shown to lower the risk of acute kidney injury (34). The risk of long-term toxicity from using furosemide should be considered in the neonates (41).

In case of polyuria associated with electrolyte losses; there should be close monitoring of serum electrolytes, especially bicarbonate, potassium, calcium and magnesium, appropriate

replacement of these losses are necessary (42). A simple approach to management of nephrotoxicity in children has been summarized below. (Figure 2.1).

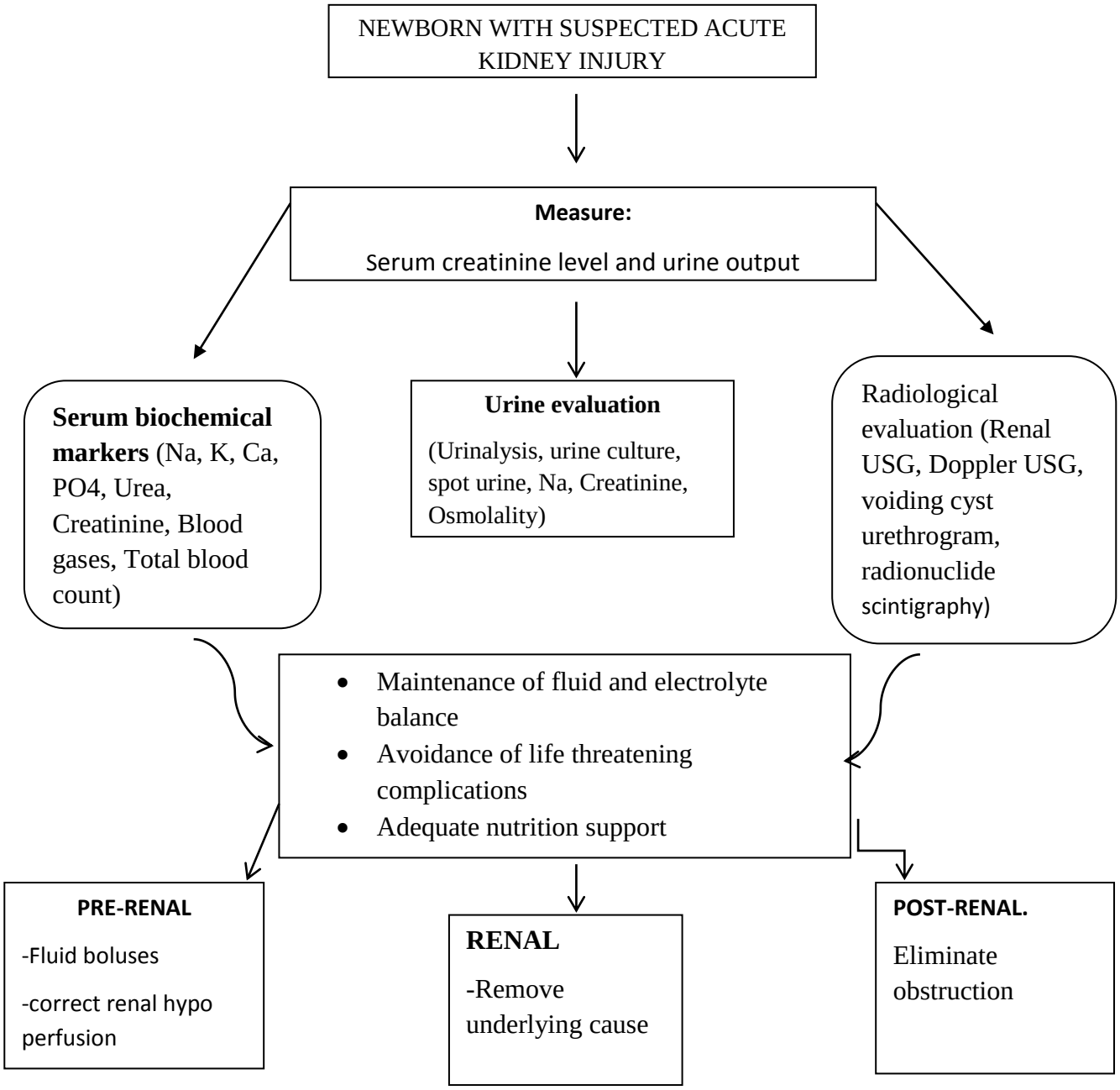


Figure 2:1. Simplified approach for management of nephrotoxicity (42).

2.8. Prevention of aminoglycoside associated nephrotoxicity.

2.8.1. Choice of aminoglycoside.

The clinician should choose the aminoglycoside with the least toxicity. The rank of nephrotoxicity of aminoglycoside has been reported to be highest-lowest as, neomycin > gentamicin > tobramicin > amikacin > netilmicin > streptomycin(3).

2.8.2. Extended interval dosing.

Extended interval dosing has been shown to be equally effective as 12 hourly dosing, with reduced risk for nephrotoxicity. A high single daily dosing of aminoglycosides increases the megalin mediated uptake of the drug at the proximal tubule resulting in a greater percentage of excretion in urine(43). A randomized control trial in the UK compared children treated with tobramycin once daily and those treated thrice daily for 14 days for cystic fibrosis, and reported that once daily dosing was significantly less nephrotoxic than thrice dosing, with an adjusted mean difference in serum creatinine change of (-8%, 95 % CI -15.7 to -0.4) (44).

2.8.3. Therapeutic drug monitoring (TDM).

TDM is essential in monitoring the aminoglycoside peak levels are high enough for effective anti- infective activity and trough levels are low enough to minimize toxicity. If done correctly, it will avoid wastage of resources and sub therapeutic levels of treatment(6).

2.8.4. Daily monitoring of serum creatinine .

Studies have recommended daily monitoring of serum creatinine levels in children to prevent nephrotoxicity. In the NINJA study (Nephrotoxic Injury Negated by Just-in-time Action) systematic screening of electronic health records was instituted to identify children receiving IV aminoglycosides for ≥3 days or ≥3 simultaneous nephrotoxins. Daily monitoring of serum creatinine was done. The mean weekly AKI rate was 25.5 % for nephrotoxin-exposed patients using the pRIFLE criteria(45) . A 42 % reduction in AKI intensity (from 33.6 to19.5 days/100 exposure days) was reported during 1 year of implementation of the screening programme. A follow-up analysis of this project after 3 years of implementation revealed that there had been a 38 % reduction in exposure to nephrotoxic medications (11.63 to 7.24 exposures/1000 patient days), and a 64 % reduction in the AKI rate (2.96 to 1.06 episodes/1000 patient days)(45)**.**

Other measures such as prevention of dehydration, sufficient nourishment may also help in reduction of nephrotoxicity in the pediatric population.

2.9. Conclusion.

In summary, there was no study done in Kenya to monitor the serum creatinine levels before and after administration of aminoglycosides in children. This study determined the incidence of nephrotoxicity in the children by measuring the serum creatinine levels before and after use of aminoglycosides in this population. The RIFLE criteria had been used in many studies to define kidney injury, and it was adopted in this study.

2.10. Conceptual framework

The main outcome measure of this study is the nephrotoxicity associated with aminoglycosides use in the pediatric population.

The risk factors of nephrotoxicity in this population include, drug related factors, patient related factors and other confounding factors.

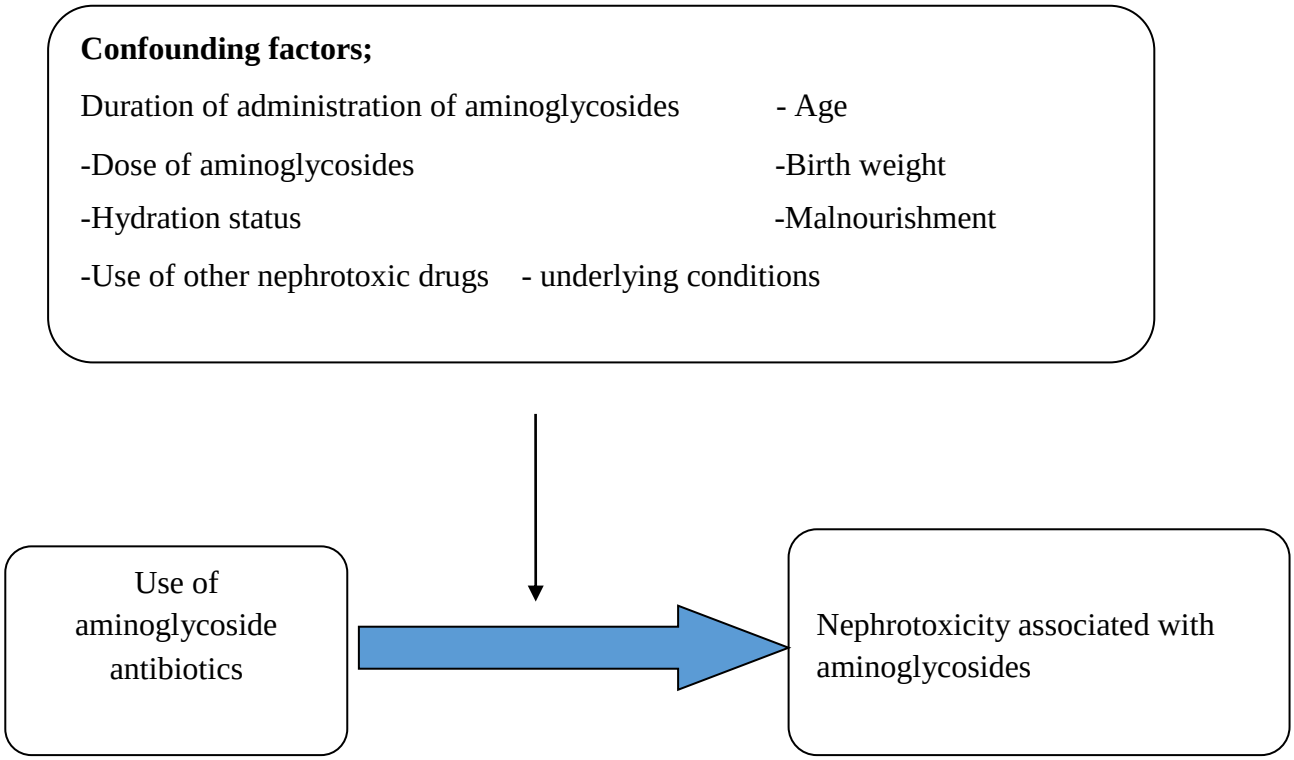


Figure 2.2: Conceptual framework for nephrotoxicity associated with aminoglycoside therapy in children.

CHAPTER 3 : METHODOLOGY

3.1. Study design.

A hospital based prospective cohort study was carried out to determine the incidence of nephrotoxicity associated with aminoglycosides use among children aged 5 years and below admitted at KNH from July to September 2018.

3.2. Study area and site.

The study was conducted at Kenyatta National Hospital (KNH) within the four general pediatric wards and the newborn unit. Kenyatta National Hospital is a national referral and a teaching hospital for the University of Nairobi, College of Health Sciences (CHS) and Kenya Medical and Training College (KMTC). It receives patients both from the low and middle-income socioeconomic classes within Nairobi and referrals from surrounding counties like Kiambu, Thika and Machakos. According to the KNH Health Management Information Systems (HMIS) report of 2017, the hospital has four general pediatric wards (3A, 3B, 3C and 3D) and it has five specialized wards that provide services to children (surgery, orthopedic surgery, oncology, ICU, renal unit, Pediatric Surgical and Renal unit). It also has a separate newborn unit (NBU). The bed capacity in pediatric wards including the newborn unit (NBU) and the special units is 336 with an average admission of 1000 new patients per month. In the year 2017, the new- born unit admitted an average of 328 neonates per month; general pediatric wards admitted the following numbers respectively (3A-138 patients, 3B-135patients, 3C-129 patients, 3D-136 patients). Special surgical ward admits -26 patients, oncology ward-7 patients and Pediatric Intensive Care Unit-10 patients respectively. Approximately 20% of the patients in the newborn unit and general pediatric wards were treated with aminoglycosides.

3.3. Study population.

The study population was children aged 5 years and below, admitted in KNH from the period of July – September 2018, and treated with aminoglycosides.

3.3.1. Inclusion and exclusion criteria.

The study included all children aged 5 years and below, admitted at the general pediatric wards and the newborn unit treated with aminoglycoside antibiotic, whose parent or guardian gave consent and those patients who had not used aminoglycosides for more than 3 hours before the baseline creatinine measurement were excluded.

Patients with existing renal malfunction (serum creatinine levels of above 70 μmol/L, those admitted to the pediatric renal unit, intensive care unit and oncology ward and those on aminoglycoside therapy for more than three hours before baseline serum creatinine measurements, were excluded from the study. Patients who were treated for less than 72 hours were also excluded from the study. Preterm neonates were excluded from the study due challanges in drawing blood in this population.

3.3.2. Sample size determination.

Sample size (n), was calculated using Fischer's formula, which is used in calculating sample size for prevalence or incidence studies (46).

$$n = \frac{z^2 \times p\,[1-p]}{d^2}$$

Whereby;

n= Minimum sample size

z= standard normal deviate for 95% confidence interval (= 1.96)

P= the estimated proportion of nephrotoxicity in children using aminoglycosides. Several studies reported different prevalence rates of nephrotoxicity and there was no study in resource-limited areas that reported the prevalence of aminoglycoside nephrotoxicity. Therefore, we used the estimated prevalence of 50% (46).

d= level of precision (set at ±5%)

$$n = \frac{1.96^2 \times 0.5(1-0.5)}{0.0025} = 384.16$$

The minimum sample size was 384 children according to Fischer's formula.

Correcting for a finite population:(46).

$$n' = \frac{NZ^2 P(1-P)}{d^2 (N-1) + Z^2 P (1-P)}$$

Where,

n' = sample size with finite population correction,

N = is the sample size before finite population correction, 384

Z = standard normal deviate for 95% confidence level at 1.96

P = Expected proportion of children on aminoglycosides who develop nephrotoxicity (50%), and

d = desired Precision (0.05)

$$=\frac{384*1.96^2*0.5(1-0.5)}{0.05^2(384-1)+1.96^2(0.5(1-0.5))}$$

=368.79/1.9179

=192.29.

The sample size was approximated to 195 children.

3.4. Recruitment and training procedure for the study assistant

A phlebotomist was recruited as a study assistant to assist in blood sample collection from the patients. He was trained on the study methodology and the schedule of specimen collection. The study assistant was instructed to draw blood and take the samples to the renal laboratory for analysis strictly as per schedule.

3.5. Sampling procedures.

Patients were sampled consecutively from the admitting wards until the sample size was achieved. The patients were followed up individually until the end of aminoglycoside therapy.

3.6. Consenting and recruiting procedure.

The children were recruited on admission from the respective admitting wards, which was on a rotational basis for the general wards 3A, 3B, 3C, and 3D. In addition, the neonates at the newborn unit were recruited on a daily basis on admission.

The researcher visited the pediatric wards daily an hour before ward rounds commenced to identify patients initiated on aminoglycoside antibiotics the previous night to start the consenting process. Patients initiated on aminoglycosides during ward rounds were recruited after the ward rounds by going through the patient files. The study procedures were well explained to the caregivers who were consented to participate in the study. Those that gave voluntary consent were screened for eligibility and enrolled.

3.7. Blood sample collection procedures.

3.7.1. Specimen collection and handling

The phlebotomist drew 2.0ml of blood into the red vacutainers without anticoagulant and filled the request forms for the urea, electrolytes and creatinine (UEC). Blood sample for baseline UEC levels was collected before administration of aminoglycosides or within three hours of administration of the first dose of aminoglycosides.

Blood sample collection for the follow up UEC's was done at completion of treatment. The samples of blood were transported at room temperature (18-25 degrees Celsius) to the renal laboratory within 20 minutes of collection.

3.7.2. Determination of serum creatinine levels

Serum creatinine levels were determined using the Cobas Integer machine available at the renal laboratory at the Kenyatta National Hospital. In this machine, creatinine reacts with picrate to produce a reddish color by Jaffa's' reaction. The intensity of red color formed is directly proportional to the creatinine concentration measured photo metrically at 500nm.

3.8. Follow up plan for the children.

The children's progress was followed up by attending the ward rounds and any relevant updates on either dose adjustment or stoppage of aminoglycoside therapy were noted. The children were followed up to completion of their aminoglycoside treatment or when they were switched to any other antibiotics.

3.9. Study variables

The dependent variable was rise in serum creatinine at completion of treatment.

The independent variables were, use of aminoglycosides.

The potential confounders were**;** patient related factors; age, birth weight, hydration status, malnourishment, underlying clinical conditions, aminoglycoside used and duration of administration of the aminoglycoside, dose, dosing schedule. drug related factors; dose and duration of treatment, concurrent use of other nephrotoxic medications, Maternal factors during pregnancy; use of nephrotoxic medication in pregnancy, chronic illness during pregnancy.

3.10. Data collection procedures

The data were collected from July to September 2018. Information on socio-demographic characteristics such as; name, gestational age at birth, weight at birth, were obtained by

interviewing the mothers and from the hospital record and documented on a data collection form. The weight on admission and date of admission was extracted from the files and documented in a data collection form.

Previous medical and medication history was obtained by interviewing the mother, guardian or from any referral letters from previous hospital attended. The urea and electrolyte levels were abstracted from the laboratory report forms and documented in the data collection form. The data on maternal characteristics such as, socio demographic factors, medical history of the mother, and history of using nephrotoxic drugs during pregnancy were collected by interviewing the mother. Data on other risk factors associated with nephrotoxicity in the neonates such as; gestational age at birth, weight at birth, perinatal asphyxia, PDA or use of NSAIDS, and maternal characteristics during pregnancy were recorded. In older children, history of admissions, chronic diseases, dehydration status, and medication history was considered.

3.11. Definition of study outcomes.

3.11.1. Primary Outcome:

The **incidence of nephrotoxicity** associated with aminoglycosides.

It was defined as kidney injury according to the pediatric RIFLE criteria.

3.11.2. Predictors.

Association of the children and maternal risk factors with nephrotoxicity, discharge status by the time of completion of aminoglycoside treatment, change to another antibiotic or death.

Age: The children were categorized according to the WHO classification:

Neonate were defined as the term babies of age 0-28 days, infants,1month-2 years , and children 2-12 years.

Birth weight: The neonates' birth weight were categorized according to the WHO's classification as; very low birth-weight <1500gms at birth, low birth-weight neonates <2500gms and normal birth-weight ≥2500- 4500gms at birth.

3.11.3. Short term outcomes of the patients on aminoglycoside therapy.

The short term outcomes of aminoglycoside therapy were defined as either stoppage of therapy due to side effects, switching to other antibiotics, discharge or death during the study period.

3.12. Data collection instruments.

Socio-demographic features for both the children and their mothers were recorded on the data collection tool.

Clinical features obtained through interviews were recorded on the data collection tool. The underlying illnesses and the current medications were obtained from the patients files. Laboratory investigations were recorded on the same data collection tool (APPENDIX 2A).

3.13. Data management.

3.13.1. Data entry, cleaning, and storage.

Data from the data collection tools were coded and entered into the EPI Info software. Data entry was done immediately after abstracting to ensure data quality. Logical checks were used to clean variables such as age and sex. Data with patient identification were stored under lock and key for confidentiality. The names of the participants were not used on data collection tools. All data were coded and stored in password protected electronic records with restricted access to ensure privacy and confidentiality.

3.13.2. Data quality assurance procedures.

A qualified phlebotomist was recruited for withdrawal of blood samples. All the blood samples for the baseline creatinine tests and follow up tests were sent to the renal laboratory at Kenyatta National Hospital for analysis to ensure uniformity of results. This renal laboratory is registered with the quality control program known as Huqas, and is subject to quality assurance audit.

Calibration of the 'Cobas Intega' machine was done using serum standard calibrator or a suitable aqueous standard. Re-calibration was done whenever preventative maintenance was performed or a critical component was replaced, or the lot number of reagents changed, and when the control values had shifted and a new control did not rectify the problem.

3.11.3. Data analysis

The STATA statistical software, version 13, was used for data analysis. Continuous variables such as gestational age, birth weight, age at admission, weight on admission were analyzed using mean, standard deviation since the population was normally distributed. Medians, interquartile range were used to summarize continuous variables that were not normally distributed. Categorical variables such as, severity of nephrotoxicity, were summarized using proportions. Multivariate analysis was done to check for association between individual risk

factors and AKI while controlling for other potential confounders in the children using aminoglycosides. ANOVA test was used to test for statistical significance for categorical variables and t-test was used to test continuous variables at a significance level of 5% with 95% confidence interval.

3.12. Ethical considerations

3.12.1. Protection of children.

The mothers or guardians of the pediatric participants were informed about the objective of the study. They were advised that their participation was highly appreciated but not mandatory. They were informed that their names would not be used on the data collection tools, and their identity would remain anonymous.

3.12.2. Minimizing interruption of services.

To minimize interruption of services, the consenting process and collection of data was carried out before and after the clinical ward rounds or when a clinician was not attending to the patients. Research samples were collected along with the routine samples to minimize frequent bleeding.

3.12.3. Protection of health records and confidentiality.

All information collected on the children was treated as confidential. Documents containing the respondent's confidential information were not reproduced nor the names of clinicians attending to them recorded. The electronic data were accessible only to the researcher, and it included no patient name and it was protected with a password to ensure no free access.

3.13. Beneficence.

3.13.1. Results for patient care

The study results obtained from the diagnostic laboratory were shared with the clinician to inform clinical decision-making.

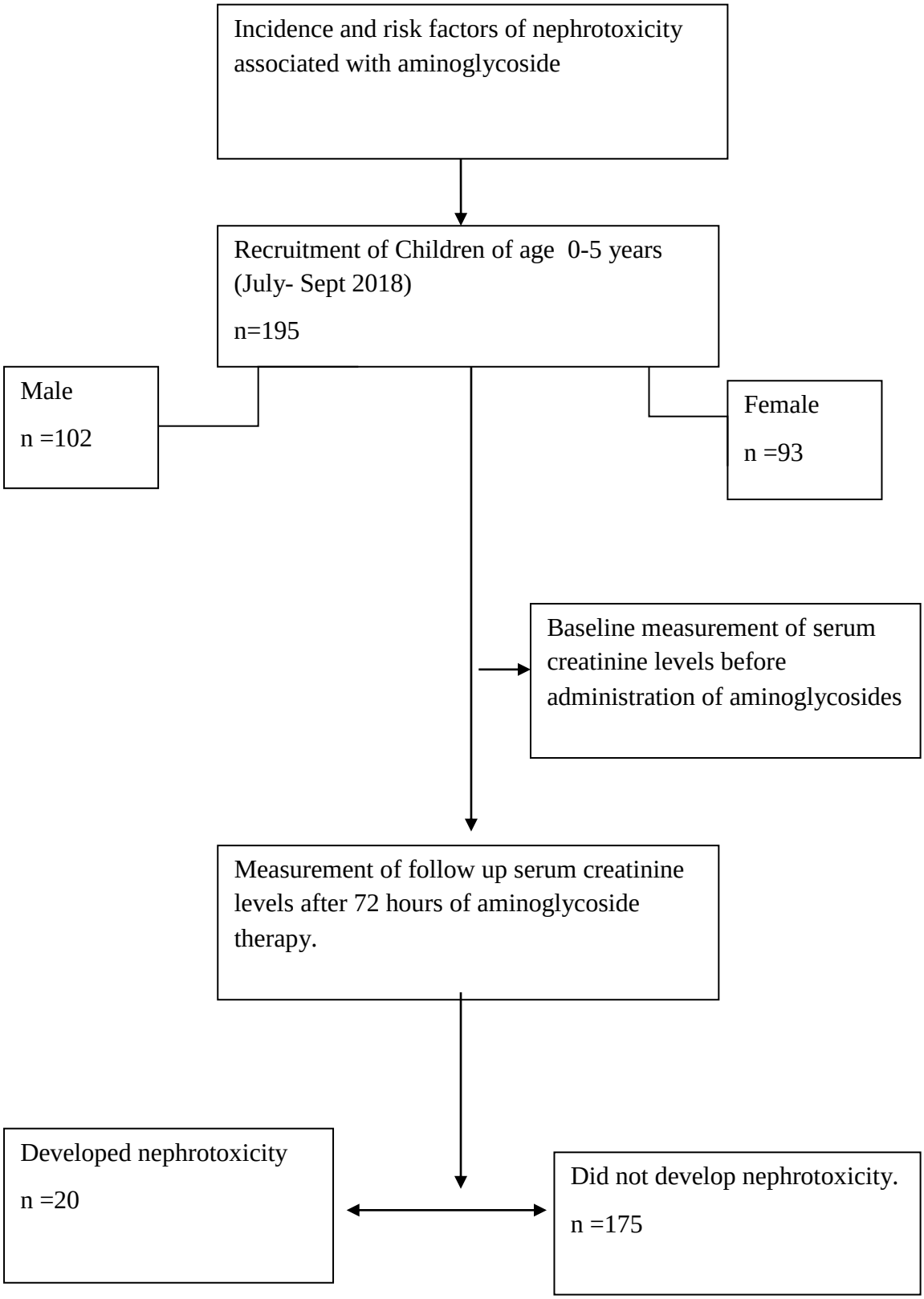
3.13.2.Ethical approval.

Ethical approval was sought from the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH-UoN ERC- approval number KNH-ERC/A/91) before initiating the study. The mothers of eligible children were given information about the study in a language they understand before their enrollment to the study. If t hey agreed to participate, they gave a voluntary written consent. (Consent form Appendix 1a and 1b).

3.13.3. Data dissemination.

The results of this study were shared with the department of Pharmacology and Pharmacognosy at the School of Pharmacy, the University library and repository. A copy of the thesis will be sent to the KNH/UoN ERC, the Kenyatta National Hospital and the supervisors of this thesis**.** The results of the study were also presented at the Association of Hospital Pharmacists, Kenya (HOPAK) symposium held in September 2019. The manuscript has been submitted for publication in a peer reviewed journal.

Figure 3:1 . STUDY FLOW CHART



CHAPTER 4 : RESULTS

4.1. Demographic characteristics of the neonates and the children on aminoglycoside therapy at KNH.

Of the 195 patients, 102 (52.3%) were male while 93 (47.7%) were female. Their median age (IQR) was 6 months (0.5-16.2). This included 58 (29.7%) neonates, most of whom, 51 (87.9%), weighed above 2500gm. Most of them were of age >28days to 2 years 107 (54.9%). The mean gestational age for the neonates was 38.2 weeks (SD 2.5). The mean weight for the neonates was 3kg (SD 1.4), while the infants weighted was 7.6kg (SD 4.8) and the children aged 2 years to 5 years 8.6 kg (SD 3.9) respectively. (Table 4.1)

Table 4:1: Demographic characteristics of the neonates and children on aminoglycoside therapy at KNH.

Characteristics	n (%)
Sex of the child	
Male	102 (52.3%)
Female	93 (47.7%)
Age categories	
Age ≤ 28 days	58 (29.7%)
Age >28 days to 2years	107 (54.9%)
Age > 2years- 5 years	30 (15.4%)
Median age (IQR) in months	6.0 (0.5-16.2)
Mean gestational age for the neonates at birth (SD) in weeks	38.2 (2.5)
weight categories in neonates	
≥2500gm	7 (12.1%)
≤2500gm	51 (87.9%)
Mean weight in kg(SD) per age categories	
Age ≤ 28 days	3.0 (1.4)
Age >28 days to 2years	7.6 (4.8)
Age > 2years- 5 years	8.6 (3.9)

4.2. Incidence of nephrotoxicity associated with aminoglycosides among children admitted at KNH (July to Sept 2018).

Of the 195 children, 20(10.25%) of them developed nephrotoxicity. (Figure 4.1)

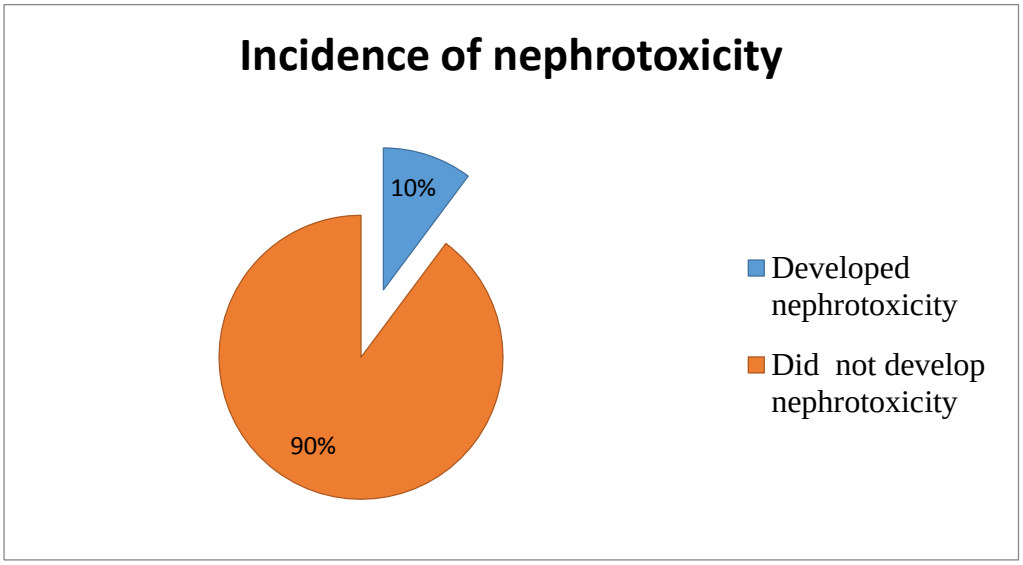


Figure 4:1. Incidence of nephrotoxicity associated with aminoglycoside use among pediatric patients (0-5yrs), admitted at KNH.

4.3. Clinical characteristics of the children on aminoglycoside therapy in KNH.

Of the 195 children, 31(15.9%) had been previously admitted, 28 (14.4%) were using medications at home for chronic diseases, while 23 (11.8%) had used nephrotoxic medication as obtained from the medication history. On admission, 61(31.3%) of them were dehydrated. The median duration for treatment with amikacin was 3 days (IQR 3.0-4.0), while for gentamicin it was 5 days (IQR 4.0-5.0). (Table 4.2).

Table 4:2. Clinical characteristics of the children on aminoglycoside therapy at KNH.

Clinical characteristic	**n (%)**
Patient dehydrated on admission	
Yes	61 (31.3)
No	134 (68.7)
Use of medication at home for chronic conditions	
Yes	28 (14.4)
No	167 (85.6)
History of nephrotoxic medication use	
Yes	23 (11.8)
No	172 (88.2)
Median(IQR) duration of treatment in days	
Amikacin	3 (3.0-4.0)
Gentamicin	5 (4.0-5.0)
Dosing interval (24 hourly)	195 (100%)
Mean follow up sodium levels(SD)	3 (5.9)
Mean change in potassium levels (SD**)**	2.2 (3.5)

4.4. Medical conditions in the children and neonates treated with aminoglycosides at KNH.

Most of the children, (117 (60%)) were diagnosed with severe pneumonia and neonatal sepsis 22 (11.3%) (Table 4.3).

Table 4:3. Medical conditions in the children treated with aminoglycosides at KNH.

Current diagnosis	**n (%)**
	117 (60.0)
	36 (18.5)
Severe pneumonia	12 (6.2)
Neonatal sepsis	11 (5.6)
Meningitis	8 (4.1)
Acute GE	11 (5.6)
Perinatal asphyxia	
Others	2 (1.0)
Aspiration pneumonia	2 (1.0)
Malnutrition	2 (1.0)
Sickle cell crisis	1 (0.5)
Anemia	1 (0.5)
Febrile neutropenia	1 (0.5)
Prematurity	1 (0.5)
Pulmonary tuberculosis	1 (0.5)

4.5. Type of aminoglycosides administered to the children at KNH.

The most commonly used aminoglycoside in the children at KNH was gentamicin 160 (82%), and amikacin 35 (18%). Figure (4.2).

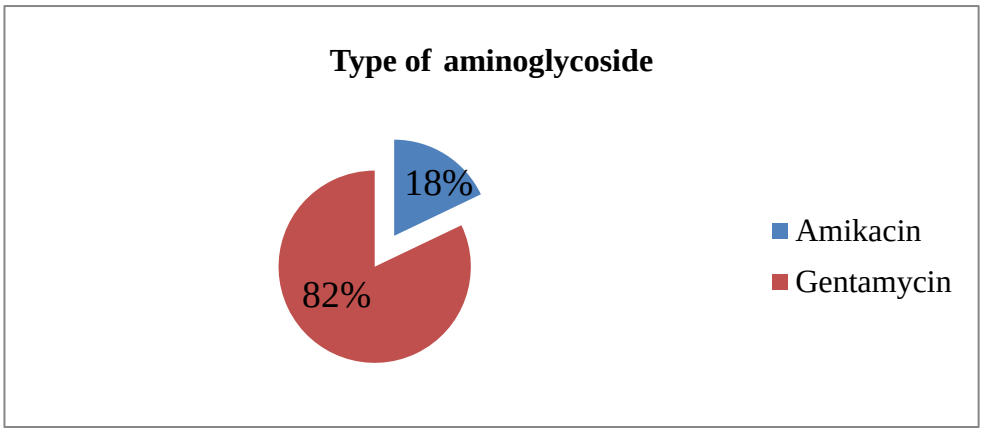


Figure 4:2. Type of aminoglycoside administered of the children on aminoglycoside therapy in KNH

4.6. List of the concurrent medications used in the children using aminoglycosides at KNH.

The children used other medications concurrently as listed below. (Table 4.4).

Table 4:4. List of the concurrent medications used among children on aminoglycosides at KNH.

List of medication history	n	Percentage
Benzyl penicillin	172	87.2
Nevirapine / zidovudine	1	0.51
Rifampicin/ Isoniazide/ Pyrazinamide and Ethambutol	1	0.51
Artesunate, Digoxin, calcium supplements	1	0.51
Calcium supplements	1	0.51
Calcium supplements, furosemide and sildenafil.	1	0.51
Calcium supplements and furosemide	1	0.51
Carbamazepine, sodium valproate, phenytoin	1	0.51
Calcium supplements, zinc sulphate, ORS	1	0.51
Folic acid hydroxy-urea	1	0.51
Furosemide sildenafil	1	0.51
Hydroxy- urea, folic acid , paracetamol	1	0.51
Nevirapine, cotrimoxazole	2	1.03
Nevirapine, zidovudine	1	0.51
Oxygen, amoxicillin, prednisolone, gentamicin	1	0.51
Oxygen, Ranferon, sodium valproate phenorbarbitone	1	0.51
Phenorbarbitone, sodium valproate	4	2.05
Phenytoin, phenorbarbitone	1	0.51
Rivotril, phenorbarbitone	1	0.51
Sildenafil, furosemide	1	0.51
Total	195	100.00

4.7. Maternal demographic characteristics

A total of 195 mothers were included in the study with a mean age of 28.4 (24-38) years. Most of them, 140 (70.8%), had attained high school level of education, 125 (64.1%) were unemployed, and 181 (92.8%) were married (Table 4.5).

Table 4:5. Maternal demographic characteristics.

Variable	**Frequency**
Mean age (years (SD))	28.4 (24-38)
Level of education	
Primary	20 (10.3%)
High school	140 (70.8%)
Tertiary level	35 (18.9%)
Employment status	
Employed	11 (5.6%)
Self employed	59 (30.3%)
Unemployed	125 (64.1%)
Marital status	
Married	181 (92.8%)
Separated/divorced	2 (0.5%)
Single	13 (6.7%)

4.8. Maternal clinical characteristics

Of the 195 mothers, 119 (92.8%), delivered their babies at the Kenyatta National Hospital. Some of the mothers, 14 (7.2%)**,** had a history of admission during pregnancy, while 30 (15.4%) of the mothers reported use of NSAIDS at least once at some point in their pregnancy. Most mothers, 182 (93.3%) did not experience any illness during pregnancy, however, 6 (3.1%) of them developed hypertension in pregnancy (Table 4.6).

Table 4:6. Maternal clinical characteristics.

Clinical characteristic	n (%)
Place of delivery	
KHN	119 (61.0)
Other facilities	74 (37.9)
Home	2 (1.0)
Admitted during pregnancy	
Yes	14 (7.2)
No	181 (92.8)
Used any NSAIDS during pregnancy	
No	16 (84.6)
Yes	30 (15.4)
History of illness during pregnancy	
Hypertension in pregnancy	6 (3.1)
Uterine tract infection	2 (1.0)
Peptic ulcer disease	1 (0.5)
HIV	1 (0.5)
Upper respiratory infection	2 (1.0)
No illness reported	182 (93.3)

The medications used in pregnancy are as listed below. (Table 4.7)

Table 4:7. List of medications used by the participants' mothers during pregnancy.

Medications used in pregnancy	n	%
No medication used	182	92.82
Tenefovir, lamivudine and nevirapine	1	0.51
Amikacin, ceftriaxone, omeprazole	1	0.51
Amoxicillin, paracetamol, cetrizine, ceftriaxone	1	0.51
Amoxicillin/ clavulanic acid, phenorbarbitone.	1	0.51
Cefuroxime	1	0.51
Erythromycin	1	0.51
Methyldopa, nifedipine	5	1.54
Omeprazole	1	0.51
Total	195	100.00

4.9. Frequency of aminoglycoside associated nephrotoxicity based on the RIFLE criteria

Of the 20 patients who experienced nephrotoxicity, 12 (60%) had mild nephrotoxicity (risk of injury), 5 (25%) of them developed acute kidney, while 3 (15%) of them experienced kidney failure (Figure 4.3).

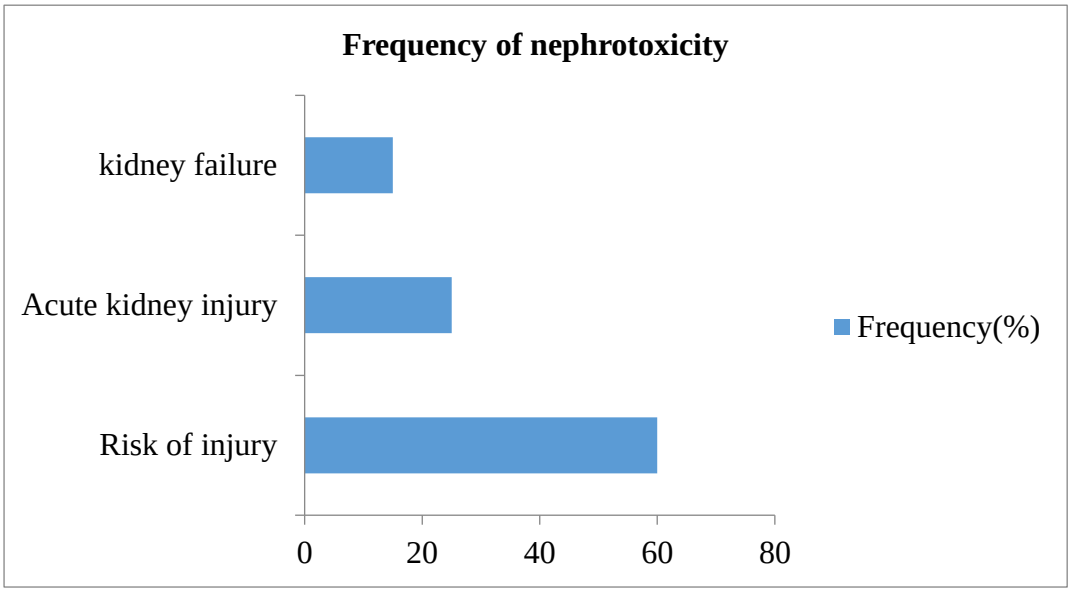


Figure 4:3. Frequency of aminoglycoside associated nephrotoxicity experienced among the children admitted in KNH during the study period.

4.10. Short-term treatment outcomes in the children treated with aminoglycosides at KNH during the study period.

The mean temperature for the 195 children recorded before treatment was 39.8(SD: 0.25) degrees Celsius, while the mean temperature after treatment was 36.51(SD: 0.68) degrees Celsius. Most of the children, 13(6.7%) who developed nephrotoxicity were switched to cephalosporin antibiotics. There was no death of children recorded during the study period. (Table 4.8)

Table 4:8. Short-term outcomes of the children treated with aminoglycosides at KNH (July-Sept 2018).

Treatment outcome	**Developed nephrotoxicity (n (%))**	
	Yes	**No**
Discharged	2 (1.0)	77 (39.5)
Switched to other antibiotics	13 (6.7)	121 (62.1)
Died	0 (0)	1 (0.5)
Continued treatment with dose adjustment	5 (2.6)	45 (23.1)

4.11. Association of the maternal demographic characteristics with aminoglycoside associated nephrotoxicity observed in their children.

There was no significant association between the maternal demographic characteristics and nephrotoxicity experienced in their children in this study. (Table 4.9).

Table 4:9. Association of maternal demographic characteristics with aminoglycoside associated nephrotoxicity in their children.

Variable	Nephrotoxicity			P value
	Yes (%)	No (%)	RR(95% CI)	
Mean age (SD)	28.0 (4.2)	28.5 (4.8)		0.682
Highest level of education				
Primary	4 (20.0)	16 (80.0)	1.5 (0.4-6.4)	0.583
High school	11 (8.0)	127 (92.0)	0.5 (0.2-1.6)	0.245
Diploma	5 (14.3)	30 (85.7)	1.0	
Occupation				
Unemployed	13 (10.7)	109 (89.3)	1.0	
Self employed	5 (8.5)	54 (91.5)	0.8 (0.3-2.4)	0.682
Employed	2 (18.2)	9 (81.8)	1.9 (0.4-9.8)	0.437
Marital status				
Married	18 (10.0)	162 (90.00)	0.4 (0.4-5.6)	0.606
Unmarried	2 (14.3)	12 (85.7)	1.0	

*significance level ($p<0.05$).

4.12. Association of the maternal clinical characteristics with aminoglycoside associated nephrotoxicity.

There was no significant association between clinical characteristics of the mothers and the children who experienced nephrotoxicity. (Table 4.10).

Table 4:10. Association between the maternal clinical characteristics and aminoglycoside associated nephrotoxicity among their children.

Maternal clinical characteristic	Developed nephrotoxicity		RR (95% CI)	P value
	Yes	No		
Place of delivery				
Other (other hospital/ home)	8(10.5)	68(89.5)	1.1(0.5-2.4)	0.93
KHN	12(10.1)	107(89.9)	1.0	
Admitted during pregnancy				
Yes	2(14.3)	12(85.7)	1.4(0.4-5.6)	0.601
No	18(9.9)	163(90.1)	1.0	
Used NSAIDs in pregnancy				
Yes	3(10.0)	27(90.0)	1.0(0.3-3.5)	1.000
No	17(10.5)	145(89.5)	1.0	
Illness during pregnancy				
HIV	0 (0)	1 (0.5)		
Hypertension in pregnancy	2 (1.0)	4 (2.0)	-	
Peptic ulcer disease	0 (0)	1 (0.5)		0.061
Upper respiratory infection	0 (0)	2 (1.0)		
No illness	18 (9.2)	164 (84.1)		

*significance level at P≤ 0.05

4.13. Association between children's demographic and clinical characteristics with nephrotoxicity.

There was a significant association found between the weight and age of the neonates and aminoglycoside induced nephrotoxicity. Those who weighed <2500gm were 4.7 (95% CI: 1.8- 12.5) times more likely to develop aminoglycoside induced nephrotoxicity as compared to those who weighed >2500gm (p= 0.002). The neonates aged ≤28 days were 3.54 (1.6-8.21) times more likely to develop aminoglycoside induced nephrotoxicity as compared to those who aged above 28 days old. (p= 0.0032). (Table 4.11)

Table 4:11. Association between the children's demographic and clinical characteristics and aminoglycoside induced nephrotoxicity.

Variable	Developed nephrotoxicity		RR (95%CI)	P value
	Yes (%)	No (%)		
Median age of the child in months	0.4 (0.2-11.2)	6.3 (0.7-16.3)		0.238
Age ≤28 days	12 (6.2)	46 (23.6)		
Age >28 days-2years	6 (4.1)	101 (66.2)	3.54 (1.6-8.21)	**0.003****
Age 2 years – 5 years	2 (0.1)	28 (14.4)		
Sex of the child				
Male	10 (9.8)	92 (90.2)	0.91(0.39-2.09)	0.827
Female	10 (10.8)	83 (89.2)		
Weight in mg				
< 2500g	3 (42.8)	4 (57.1)		
≥ 2500g	17 (9)	171 (91)	4.73(1.8-12.5)	**0.002****
Patient dehydrated on admission				
Yes	6 (9.8)	55 (90.2)	0.94 (0.38-2.33)	0.896
No	14 (10.4)	120 (89.6)		
History of previous admissions				
Yes	1 (3.2)	30 (96.8)		
No	19 (11.6)	145 (88.4)	0.27 (0.04-2.0)	0.204
Use of any concurrent nephrotoxic medication				
Yes	1 (4.3)	22 (95.7)	0.39 (0.1-2.8)	0.352
No	19 (11.0)	153 (89.0)		
Median duration of treatment (IQR)				
Amikacin	3.0 (3.0-3.5)	3.0 (3.0-4.0)	-	0.211
Gentamicin	5.0 (4.0-5.5)	5.0 (4.0-5.5)		
Aminoglycoside used				
Amikacin	2 (1.03)	32 (16.41)	0.52 (0.13-2.16)	0.367
Gentamicin	18 (9.23)	141(72.31)		

Significance level P≤0.05

4.14. Association between the underlying conditions in the children treated with aminoglycosides and development of nephrotoxicity.

Among the neonate, those treated for neonatal sepsis were 4.91(2.07-11.62) times more likely to develop nephrotoxicity than those who were treated for other conditions (P=0.001). There was no significant association between the other underlying illnesses and development of nephrotoxicity in the children. (Table 4.12).

Table 4:12. Association between the underlying medical conditions and aminoglycoside induced nephrotoxicity.

Diagnosis	**Nephrotoxicity**		**RR (95% CI)**	**P value**
	Yes (%)	**No (%)**		
Neonatal sepsis (age ≤28 days)				
Yes	15 (25.8)	7(12.1)	4.91(2.07-11.62)	**<0.001****
No	5 (8.6)	31(53.4)	1.0	
Severe pneumonia				
Yes	9 (7.7)	108 (92.3)	0.5 (0.2-1.3)	0.154
No	11 (14.1)	67 (85.9)	1.0	
Meningitis				
Yes	0 (0)	12 (100.0)	0.345(0.02-5.39)	0.448
No	20 (10.9)	163 (89.1)		
Acute Gastro enteritis				
Yes	2 (18.2)	9 (81.8)	1.85 (0.49-7.01)	0.360
No	18 (9.8)	166 (90.2)		
Perinatal asphyxia in neonates(age ≤28 days)				
Yes	4 (6.9)	4 (6.9)	1.56 (0.70-3.48)	0.275
No	16 (27.6)	34(58.6)		
Others.				
Yes	0	11 (100.0)	0.3(0.02-5.84)	0.484
No	20 (10.9)	164 (89.1)		

Significance p≤0.05

4.15. Classification of aminoglycoside induced nephrotoxicity.

Most patients 13 (65%), significantly experienced a risk of kidney injury which was mild and reversible (P=0.001), 4 (20%) experienced acute kidney injury, while 3(15%) of them experienced kidney failure as defined by the pediatric RIFLE criteria. (Table 4.13).

Table 4:13. Classification of the aminoglycoside induced nephrotoxicity.

Severity of injury	**Nephrotoxicity**		**P value**
	Yes	**No**	
Risk of injury	13 (65%)	7 (35%)	
Acute kidney injury	4 (20%)	16 (80%)	**0.001****
Kidney failure	3 (15%)	17 (75%)	

Significance p≤0.05.

CHAPTER 5 : DISCUSSION AND CONCLUSION.

Aminoglycosides are filtered at the glomerulus and transported into the proximal tubular cell lysosome by endocytosis, leading to tubular cell necrosis via several mechanisms. Based on the RIFFLE criteria, we established a 10.25% incidence of aminoglycoside nephrotoxicity in this population. This finding is consistent with studies done in the last 10 years which showed the rates of aminoglycoside associated nephrotoxicity to range between 3% to 35% (12,47). The nephrotoxicity experienced in the children was mostly mild and reversible, as 65% of the cases had a risk of injury as categorized by the RIFLE criteria (P=0.001). This was consistent with most studies that described aminoglycoside induced nephrotoxicity as mild and reversible.(7,17,18).

Neonatal age was significantly associated with nephrotoxicity, (P= 0.0032). This is because the neonates' kidneys are still considered immature and hence they are predisposed to acute kidney injury (48). Using nephrotoxic medication in this population increases the risk of kidney injury, especially if not used cautiously. For instance, a retrospective study of gentamicin exposure in a U.S centre reported a prevalence of 26.2% of nephrotoxicity (3). However, a Cochrane review of seven retrospective controlled studies including 1321 newborn infants, found that nephrotoxicity was rare in this population, although, one of the studies observed an elevated N-acetyl-beta-glucosaminidase excretion rate in gentamicin-treated infants (49). A study of 90 infants using aminoglycosides for a mean duration of 9 days observed no nephrotoxicity during the study period. This variation may be attributed to the variations in kidney injury definitions (50).

Low birth-weight of the neonates was significantly associated with aminoglycoside nephrotoxicity (p= 0.012). Similar studies have found a prevalence of AKI of 34.5% and 79% in the low birth-weight neonates (8,28). A study done on short term outcomes of AKI on neonates with perinatal asphyxia in KNH, however, found no significant association between low birth-weight and acute kidney injury, however the effect of aminoglycosides on this population was not documented.(32)

Among the neonates of age below 28 days, those treated for neonatal sepsis in the study were 13.29 (95% CI: 3.61-48.89) times more likely to develop nephrotoxicity than those who were treated for other conditions (p=0.001). Studies have shown sepsis to be an independent risk factor for development of AKI. Mathur et al observed 200 term neonates with sepsis of whom 52 (26%) developed AKI (51)

Perinatal asphyxia was not significantly associated with nephrotoxicity observed among the neonates of age below 28 days. This finding was contrary to other studies that have shown perinatal asphyxia as an independent risk factor for acute kidney injury in the neonates with a prevalence rate of 7-72%, (21,44). A study done in the same setting at Kenyatta National hospital in 2006, found a prevalence of acute kidney injury of 11.7% in the asphyxiated neonates (32). However, the numbers of asphyxiated neonates was 8 (13.8%), which was low, and more studies with larger sample size are required to confirm this as it did not base the sample size on evaluation for individual risk factors. There was no significant association between the other underlying illnesses such as upper respiratory illness, acute gastro enteritis, meningitis, and development of nephrotoxicity in the children.

The median duration of treatment at KNH for this population was 5 days for gentamicin and 3 days for amikacin. A duration of more than seven days of aminoglycoside therapy significantly increases the risk of nephrotoxicity in children (17,19,54). All the 195 children were treated with 24 hourly extended dosing. This study did not find significant association between the duration of treatment and dosing interval with development of nephrotoxicity. Similar studies have shown that the 24 hourly dosing is as effective as 12 hourly dosing, with minimized toxicity, better adherence and reduced bacteriological failure.(34,36,55,56).

The maternal characteristics were not significantly associated with acute kidney injury. Some studies have recommended that, a large sample size will be needed in order for an association to be detected between the maternal characteristics and aminoglycoside induced nephrotoxicity (19,32). Some studies however, found that the mothers of the infants with renal injury received more drugs during pregnancy, especially antibiotics and NSAIDS.(19,27)

In this study, the patients were followed up only for the period they were on aminoglycoside treatment. The mean temperature for the 195 children recorded before treatment was 39.8 (SD: 0.25) degrees Celsius, while the mean temperature after treatment it was 36.51371 (SD: 0.68) degrees Celsius. This indicates that the treatment was effective considering the average temperature change. Of the patients who developed nephrotoxicity, 15 (75%) were switched to other antibiotics while 5 (25%) of them continued with treatment with adjustments according to the KDIGO guidelines. The mortality rate in this group, during the study period, was zero.

CONCLUSION

The incidence of aminoglycoside induced nephrotoxicity was found to be 10%. Neonates were at a higher risk of developing nephrotoxicity as compared to other pediatric patients. The low birth-weight neonates and those with sepsis were also at a higher risk of developing nephrotoxicity. Maternal factors and other patient related risk factors like perinatal asphyxia, meningitis, duration of treatment with aminoglycosides were not associated with nephrotoxicity. Most of the children were switched to cephalosporin antibiotics upon suspicion of nephrotoxicity. There was no mortality recorded during the study period.

RECOMMENDATIONS

It is recommended that aminoglycosides should be used with caution in high-risk populations like the neonates, especially those with low birth-weight, asphyxia and neonatal sepsis. Routine monitoring of kidney functions should be done in all neonates using aminoglycosides after 72 hours of therapy since they are at a higher risk of developing nephrotoxicity. Larger studies are needed to correlate maternal factors and other patient related risk factors such as perinatal asphyxia with nephrotoxicity, and to assess the long-term outcomes of the patients who develop aminoglycoside-associated nephrotoxicity.

STUDY STRENGTHS

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STUDY LIMITATIONS

The study was unable to generate correlates and risk factors due to the small sample size.

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APPENDIX Ia: CONSENT FORM

INCIDENCE AND RISK FACTORS OF NEPHROTOXICITY ASSOCIATED WITH AMINOGLYCOSIDES THERAPY AMONG PEDIATRIC PATIENTS ADMITTED IN KENYATTA NATIONAL HOSPITAL.

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Investigators' Statement:

This is to request you and your child to kindly participate in this research study. This consent form provides you with the information you will need to help you decide whether to participate or not in the study. This process is known as 'Informed Consent'. Please read this consent information carefully and ask any questions or seek clarification on any matter concerning the study. Thank you.

Introduction:

The purpose of this study is to find out the proportion of children who develop kidney injury while on treatment with aminoglycosides (gentamicin or amikacin) at Kenyatta National Hospital.

Background:

Aminoglycoside antibiotics have been in common use in newborns for treatment of neonatal sepsis, meningitis, burns together with other antibiotics and in older children for treatment of acute respiratory infections, intra-abdominal infections and complicated urinary infections. They are effective against a wide range of bacteria. They are widely used because they are well tolerated, affordable and easily available. However, they have one of the side effects that has been observed is kidney injury which in most cases is reversible.

Benefits:

All the results of the study, both normal and abnormal, will be communicated with the clinician treating the child. This will help the doctor to manage the child appropriately depending on the kidney function test results. The sponsors of this study will pay for the tests that are not routinely done in the hospital.

Risks/ harms:

The procedure will involve drawing 2.0mls of blood from children, or 1.0 ml for newborns, this will be a little painful, but a trained professional will do it. As much as possible, this procedure shall be in cooperated into the routine drawing of blood for other tests to avoid added pain to your child.

Voluntariness:

You will be free to participate or withdraw from the study at any point. Refusal to participate will not compromise your child's care in any way.

Confidentiality:

The information obtained about your newborn child, you and your family will be kept in strict confidence. The test results will be shared with the clinician for clinical care. The research team, will discuss general overall findings regarding all patient assessed but nothing specific regarding your child's condition.

Your name or that of your child will not be used on the data collection instrument. You will be given identification numbers which will be used instead. Filled data collection forms will be locked in a cupboard and will be accessible only to the research team members. Electronic data will be kept under a password. All raw data will be destroyed after data analysis and report writing.

Compensation.

There will be no payments for you to participate in this study. The study will be carried out during the time your child is admitted in the hospital. However, we will pay for the kidney function tests that are not routinely in the hospital; the kidney function test at an interval of 72 hours of aminoglycoside therapy.

Problems or Questions:

If you ever have any questions about the study or about the use of the results you can contact the principal investigator,

Dr. EMMAH NYABOKE ONG'ERA.

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If you have any questions on your rights as a research participant you can contact the Kenyatta National Hospital Ethics and Research Committee (KNH- ESRC) by calling 2726300 Ext. 44102.

B] CONSENT FORM:

Participant's Statement:

I_____ having received adequate

Information regarding the study procedures, risks, and benefits hereby AGREES to participate in the study with my child. I understand that our participation is voluntary and that I am free to withdraw at any time. 1 have been given an adequate opportunity to ask questions and seek clarification on the study and these have been addressed satisfactorily.

Signature/thumb print: _____ Date _____

Witness(relative/other patient)_____Signature/thumb print_____

Date_____

Investigators statement:

I_____ declare that I have adequately explained to the above participant, the study procedure, risks, and benefits and given him /her time to ask questions and seek clarification regarding the study. I have answered all the questions raised to the best of my ability.

Interviewers Signature _____ Date

_____

APPENDIX I b: FOMU YA KUKUBALI

VISA NA HATARI ZINAZOSABABAISHWA NA KUATHIRIWA KWA FIGO NA MATIBABABU YA DAWA YA AINA YA 'AMINOGLYCISIDES' MIONGONI MWA WATOTO WALIOLAZWA HOSPITALI YA KITAIFA YA KENYATTA

Chuo:

Chuo Kikuu cha Nairobi, kitengo cha Famasia.
Idara ya Famakolojia na Famakognosia,

Sanduku la Posta 30197-00400 Nairobi.
Nambari ya simu: 0204915027

Mtafiti:

Daktari Emma Nyaboke Ong'era

Idara ya Famakolojia na Famakognosia
Kitengo cha Famasia cha Chuo Kikuu cha Nairobi.

Wasimamizi:

1. Profesa A.N Guantai
   Idara ya famakolojia na famakognosia
   Kitengo cha famasia cha chuo Kikuu cha Nairobi.
2. Daktari Margaret Oluka
   Idara ya famakolojia na famakognosia
   Kitengo cha famasia cha chuo Kikuu cha Nairobi.
3. Daktari Beatrice Mutai
   Idara ya wagonjwa, matibabu na afya ya watoto,
   Chuo Kikuu cha Nairobi.

Thibitisho La mtafiti:

Nakuomba wewe na mtoto wako kushiriki katika utafiti huu. Fomu hii ya kukubali kushiriki itakupa ujumbe wote utakaohitaji ili kuamua iwapo utashiriki katika utafiti huu au la. Utaratibu huu unaitwa maelezo ya kukubali. Tafadhali, usome ujumbe wote kwa makini na uulize maswali yoyote au ufafanuzi wowote kuhusu utafiti huu. Asante.

Utangulizi:

Lengo la utafiti huu ni kupata idadi ya watoto wanaopata majeraha ya figo wanapoendelea kupata matibabu ya 'Aminoglycosides' katika damu katika hospitali kuu ya Kenyatta.

Kiini:

Aina hii ya dawa za kuua bakteria 'Aminoglycosides' miongoni mwa watoto wachanga zimekuwa na matumizi mengi. Miongoni mwa matumizi haya ni kama kama kudhibiti joto mwilini katika, kutibu magonjwa ya uti wa mgongo na ubongo na kuchomeka. Miongoni mwa watoto wakubwa kidogo, hutibu kuumwa na tumbo, shida za kupumua na shida za kukojoa. Dawa hizi zinatumiwa sana kwa sababu mwili huzikubali, si ghali na zinapatikana kwa urahisi. Hata hivyo, kuna athari moja kwa figo ambayo imedhihirika na inaweza kurekebishwa ikipatikana.

Utafaidi aje kwa utafiti huu?

Matokeo yote ya utafiti huu; mazuri na mabaya yatawasilishwa kwa mhudumu wa kiafya anayemtibu mtoto. Hii itamwezesha daktari kumtibu mtoto kulingana na matokeo ya vipimo vya figo na ufanyikazi wake. Wadhamini wa utafiti huu watalipia vipimo vyote ambavyo kwa kawaida havifai kufanywa hospitalini.

kuna hatari / madhara kwa mtoto atakayehusishwa utafiti huu?

Utaratibu huu utahusisha kutoa mililita mbili za damu kutoka kwa mtoto wako ambapo mtoto atahisi uchungu kiasi lakini jambo hili litafanywa na mtaalamu aliyehitimu. Utaratibu huu kwa kiasi kikubwa utakuwa kama utoaji damu wa kawaida unaofanywa wakati wa vipimo vingine ili kuepuka kusababisha uchungu zaidi kwa mtoto.

kuna shida nikikataa kushiriki utafiti huu?

Una uhuru wa kuamua kushiriki au kujitoa katika utafiti huu wakati wowote au katika hatua yoyote. Maamuzi ya kuamua kutoshiriki hayatasababisha kutohudumiwa kwa mtoto wako.

Usiri:

Ujumbe wowote kuhusu mtoto wako, wewe au familia yako utahifadhiwa kisiri. Hakuna ujumbe wowote kukuhusu, kumhusu mtoto wako au familia utawekwa wazi kwa mtu yeyote. Hata hivyo, timu hii inayofanya utafiti huu itajadiliana kwa ujumla matokeo ya utafiti kuhusu wagonjwa waliotathminiwa lakini hakuna lolote litakalojadiliwa kuhusu hali ya mtoto wako. Jina lako au la mtoto halitatumika popote katika utafiti huu. Fomu zote zenye data ya utafiti huu zitafungiwa katika kabati na zitaweza kufikiwa tu na timu iliyofanya utafiti huu. Data za kielektroniki zitafungwa kwa nywila. Data ghushi zote zitahariwa baada ya ripoti kuandikwa.

Kuna faida nikishiriki utafiti huu?

Hutalipwa kwa kushiriki katika utafiti huu. Utafiti huu utafanywa wakat mwanao amelazwa hospitalini. Hata hivyo, tutalipia vipimo vya figo ambavyo kwa kawaida havifanywi hospitalini.

Matatizo au maswali :

Iwapo utakuwa na maswali yoyote kuhusu utafiti huu au matokeo ya uchunguzi huu, wasiliana na Mtafiti mkuu

Daktari Emma Nyaboke Ong'era
Idara ya Famakolojia na Famakognosia
Kitengo cha Famasia cha chuo Kikuu cha Nairobi
0716496997.

Au

Profesa A. N Guantai
Idara ya Famakolojia na Famakognosia

Kitengo cha Famasia cha chuo Kikuu cha Nairobi
0722636427.

Au

Daktari Margaret Oluka
Idara ya famakolojia na famakognosia
Kitengo cha famasia cha chuo Kikuu cha Nairobi
0722604216.

Au

Daktari Beatrice Mutai

Idara ya wagonjwa, matibabu na afya ya watoto,

Chuo Kikuu cha Nairobi.
0708552999.

Iwapo una maswali kuhusu haki zako kama mshiriki katika utafiti huu, unaweza kuwasiliana na Kamati ya Hadhi na Utafiti ya hospitali kuu ya Kenyatta kwa kupiga Nambari 2726300.

B. FOMU YA KUKUBALI

Thibitisho la mshiriki,

Mimi_____baada ya kupokea maarifa ya kutosha yanayohusiana na utafiti huu, hatari zilizopo na manufaa yake, nakubali kushiriki katika utafiti huu pamoja na mtoto wangu. Naelewa kuwa kushiriki kwetu ni kwa hiari na nina uhuru wa kujitoa wakati wowote. Nimepatiwa nafasi ya kutosha ya kuuliza maswali na kufafanuliwa kuhusu utafiti huu na masuala haya yameelezewa nilivyotarajia.

Sahihi / chapa ya kidole gumba _____. Tarehe _____

Sahihi ya shahidi /chapa ya kidole gumba _____Tareh_____

Thibitisho la mtafiti:

Mimi _____ nadhibitisha ya kwamba nimemuelezea kwa upana mshiriki, na nimempa wakati akauliza maswali kuhusu utafiti huu. Nimejibu maswali yake yote kadhiri ya uwezo wangu.

Sahihi / chapa ya kidole gumba _____ Tarehe _____

APPENDIX II: DATA COLLECTION TOOL.

TITLE: INCIDENCE AND RISK FACTORS OF NEPHROTOXICITY ASSOCIATED WITH AMINOGLYCOSIDE THERAPY AMONG PEDIATRIC PATIENTS ADMITTED AT KENYATTA NATIONAL HOSPITAL.

Serial no: _____

Date_____

SECTION 1: SOCIAL DEMOGRAPHIC CHARACTERISTICS

Instructions:

The study assistant will read the questions to you.

Please listen carefully before answering and ask questions where you do not understand.

(Tick where applicable)

a) **Pediatric patient**

1. Age (months / years) .....
2. Gender: Male [ ] Female [ ]
3. Weight (kg) .....
4. Height (cm) .....

b). Mother

5. Age (years) .....
6. Marital status: Married [ ] Single [ ] Divorced [ ]
7. Highest level of education: Primary [ ] High school [ ]
   Diploma [ ] Degree [ ]
8. Occupation Employed [ ] Unemployed [ ] Self-employed [ ]

SECTION 2: CLINICAL CHARACTERISTICS

Mother's clinical characteristics.	[redacted]	
Caregiver other than the mother	[1] father [2] sibling [3] grandparent [4] other, specify	
If you are the mother, please continue to answer the following,	[redacted]	
Did you attend antenatal clinic visits?	[0] NO [1] YES	
If yes, how many antenatal clinics did you attend?	[1] 1 [2] 2 [3] 3 [4] I can't remember	
Where did you deliver your baby?	[1] Home [2] KNH [3]other facility [4] Other, (specify).....	
Did you get admitted in the hospital during pregnancy?	[0] NO [1] YES	Date.....duration.....
If yes, list the medication you used during admission		[ ] can't remember
Did you ever use ibuprofen during pregnancy?	[0]NO [1]YES [2] Don't know	[redacted]

Clinical characteristics of the Pediatric patient

What was the weight at birth? (mg)		
What was the gestational age at birth? (weeks)		
Has your child been admitted in the hospital before?	YES [1]	NO[0]
Does your child take medication for any existing disease?	YES[1]	NO[0]
List any medications used previously, before admission		Recommendation
What is the current diagnosis?		
Dehydration status	Dehydrated[1]	Not dehydrated[0]
List of current medication prescribed	Dose	duration
Tick the aminoglycoside prescribed	Gentamycin[1]	Amikacin[2]

SECTION 3: LABORATORY INVESTIGATIONS

Test	Results	Date done	Hours after administration of aminoglycoside	E GFR
Baseline				
Urea				
serum …				
creatinine				
1st interval of 72 hrs(day 3)				
Urea				
Electrolytes				
Serum creatinine				
2nd 72 hours interval (day 6)				
Urea				
electrolytes				
Serum creatinine				
3rd 72hours interval (day 9)				
Urea				
electrolytes				
Serum creatinine				
Outcome after aminoglycoside therapy(tick one)	Discharged [2]	Switched to other antibiotic [1]	Died [0].	

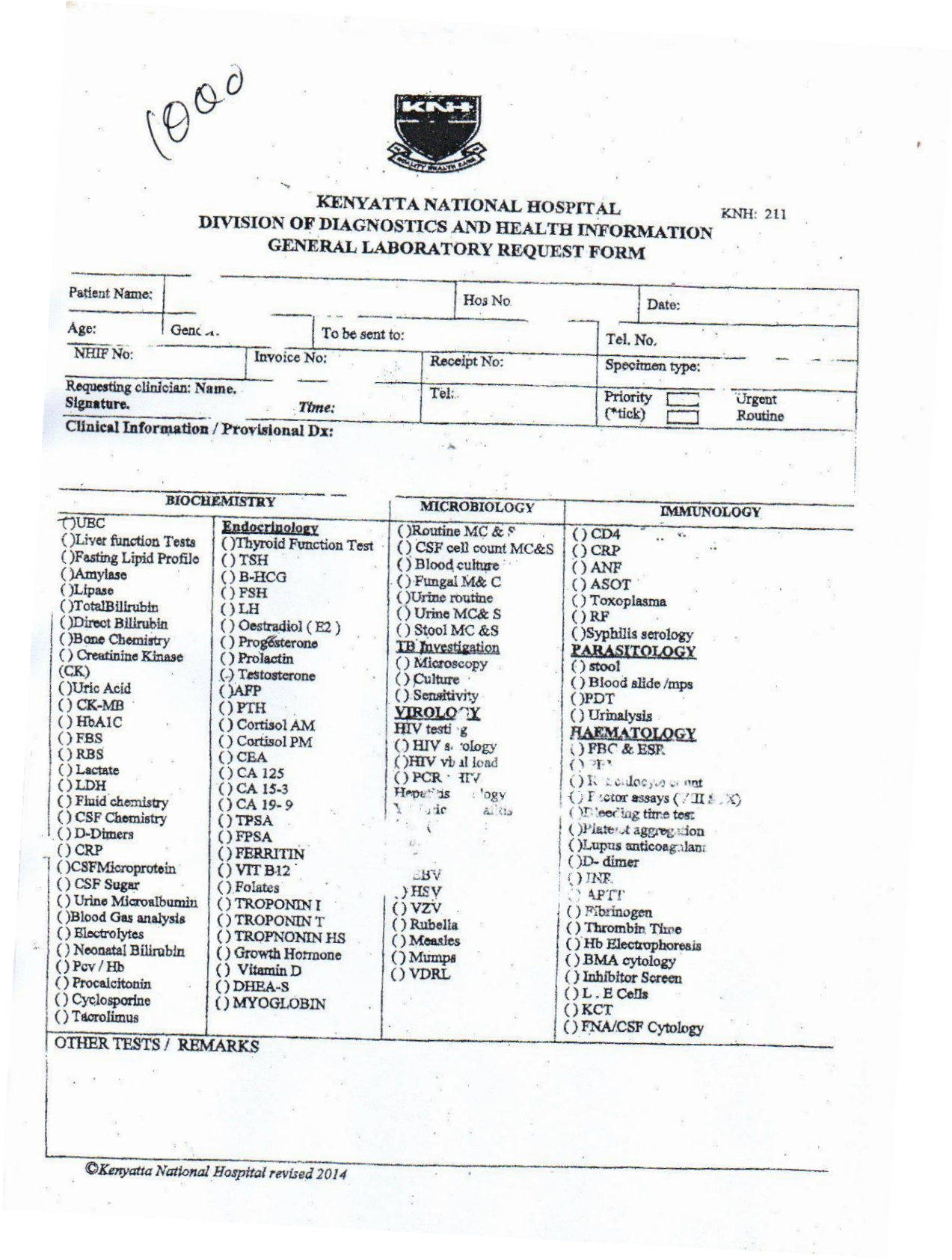
Entered by.....date.....

Checked

by.....date.....

THANK YOU FOR YOUR CO-OPERATION.

APPENDIX III: LABORATORY REQUEST FORM.



1000

KENYATTA NATIONAL HOSPITAL KNH: 211
DIVISION OF DIAGNOSTICS AND HEALTH INFORMATION
GENERAL LABORATORY REQUEST FORM

Patient Name:		Hos No	Date:
Age:	Gend .	To be sent to:	Tel. No.
NHIF No:	Invoice No:	Receipt No:	Specimen type:
Requesting clinician: Name. Signature. Time:		Tel:	Priority (*tick) ☐ Urgent ☐ Routine

Clinical Information / Provisional Dx:

BIOCHEMISTRY

( )UEC
( )Liver function Tests
( )Fasting Lipid Profile
( )Amylase
( )Lipase
( )TotalBilirubin
( )Direct Bilirubin
( )Bone Chemistry
( ) Creatinine Kinase (CK)
( )Uric Acid
( ) CK-MB
( ) HbA1C
( ) FBS
( ) RBS
( ) Lactate
( ) LDH
( ) Fluid chemistry
( ) CSF Chemistry
( ) D-Dimers
( ) CRP
( )CSFMicroprotein
( ) CSF Sugar
( ) Urine Microalbumin
( )Blood Gas analysis
( ) Electrolytes
( ) Neonatal Bilirubin
( ) Pcv / Hb
( ) Procalcitonin
( ) Cyclosporine
( ) Tacrolimus

Endocrinology

( )Thyroid Function Test
( ) TSH
( ) B-HCG
( ) PSH
( ) LH
( ) Oestradiol (E2)
( ) Progesterone
( ) Prolactin
( ) Testosterone
( )AFP
( ) PTH
( ) Cortisol AM
( ) Cortisol PM
( ) CEA
( ) CA 125
( ) CA 15-3
( ) CA 19- 9
( ) TPSA
( ) FPSA
( ) FERRITIN
( ) VIT B12
( ) Folates
( ) TROPONIN I
( ) TROPONIN T
( ) TROPNONIN HS
( ) Growth Hormone
( ) Vitamin D
( ) DHEA-S
( ) MYOGLOBIN

MICROBIOLOGY

( )Routine MC & S
( ) CSF cell count MC&S
( ) Blood culture
( ) Fungal M& C
( )Urine routine
( ) Urine MC& S
( ) Stool MC &S

TB Investigation

( ) Microscopy
( ) Culture
( ) Sensitivity

VIROLOGY

HIV testing
( ) HIV serology
( )HIV viral load
( ) PCR - HIV
Hepatitis ology
( )
EBV
) HSV
( ) VZV
( ) Rubella
( ) Measles
( ) Mumps
( ) VDRL

IMMUNOLOGY

( ) CD4
( ) CRP
( ) ANF
( ) ASOT
( ) Toxoplasma
( ) RF
( )Syphilis serology

PARASITOLOGY

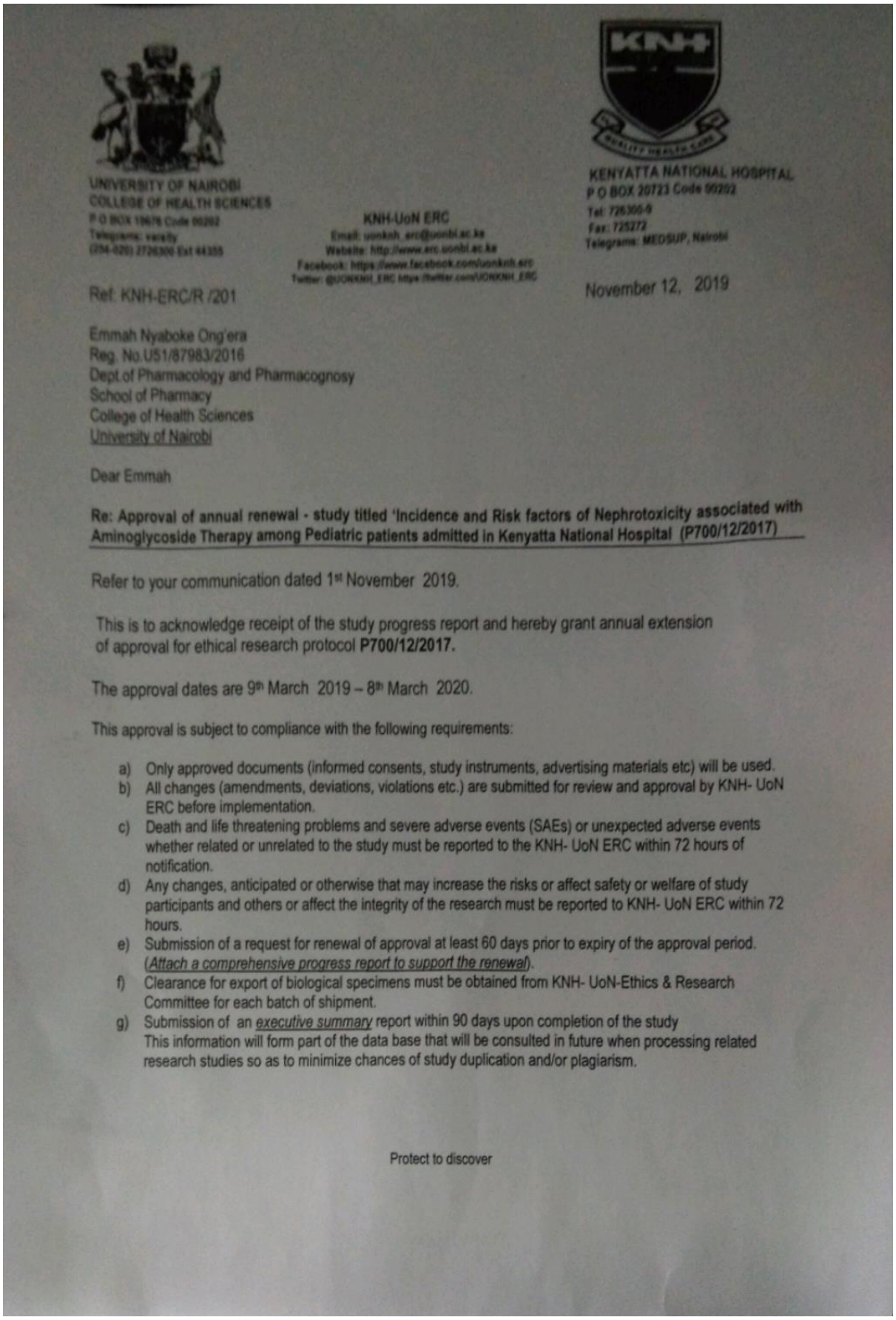
( ) stool
( ) Blood slide /mps
( )PDT
( ) Urinalysis

HAEMATOLOGY

( ) FBC & ESR
( )
( ) Reticulocyte count
( ) Factor assays (VIII IX)
( )Bleeding time test
( )Platelet aggregation
( )Lupus anticoagulant
( )D- dimer
( ) INR
APTT
( ) Fibrinogen
( ) Thrombin Time
( ) Hb Electrophoresis
( ) BMA cytology
( ) Inhibitor Screen
( ) L . E Cells
( )KCT
( ) FNA/CSF Cytology

OTHER TESTS / REMARKS

APPENDIX IV: KNH-UON ERC APPROVAL LETTER.



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Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/R /201

November 12, 2019

Emmah Nyaboke Ong'era
Reg. No.U51/87983/2016
Dept.of Pharmacology and Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Emmah

Re: Approval of annual renewal - study titled 'Incidence and Risk factors of Nephrotoxicity associated with Aminoglycoside Therapy among Pediatric patients admitted in Kenyatta National Hospital (P700/12/2017)

Refer to your communication dated 1st November 2019.

This is to acknowledge receipt of the study progress report and hereby grant annual extension of approval for ethical research protocol **P700/12/2017.**

The approval dates are 9th March 2019 – 8th March 2020.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH- UoN ERC before implementation.
c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH- UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH- UoN-Ethics & Research Committee for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study
This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

Protect to discover

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M.L. CHINDIA
SECRETARY, KNH-UON ERC

c.c. The Principal, College of Health Sciences, UoN
The Director CS, KNH
The Chairperson, KNH-UoN ERC
The Dean, School of Pharmacy, UoN
Supervisors: Prof. A.N. Guantai, Dr. Margaret Oluka, Dr. Beatrice Mutai

Thesis - INCIDENCE AND RISK FACTORS FOR NEPHROTOXICITY ASSOCIATED WITH AMINOGLYCOSIDE THERAPY AMONG HOSPITILIZED CHILDREN AT KENYATTA NATIONAL HOSPITAL

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