THE INCIDENCE OF ACUTE KIDNEY INJURY AMONGST VERY LOW BIRTH WEIGHT NEONATES IN THE NEONATAL UNIT AT UNIVERSITAS ACADEMIC HOSPITAL DURING THE PERIOD OF JANUARY 2016 TO JUNE 2016

BY

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DECLARATION

I, Princess Zinzile Ngwenyama, declare that the mini-dissection that I herewith submit in a publishable manuscript format for the Master's Degree qualification at the University of Free State is my independent work and that I have not previously submitted it for a qualification at another Institution of Higher Education.

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INDEX

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

ABSTRACT

Background. Acute kidney injury is common amongst patients admitted in neonatal intensive care. It is associated with mortality and mobility especially in very low birth weight infants. We diagnose and define Acute kidney injury using the kidney disease improving global outcomes guidelines and looked at the incidence especially before two weeks of age.
Objectives. The main objective of this study is to determine the incidence of Acute Kidney injury in Very low birth neonates admitted at neonatal intensive care unit of the Universitas Academic Hospital, from January 2016 to June 2016. Using recent proposed neonatal Acute kidney Injury classifications by Kidney disease: Improving Global Outcomes workgroup definition modified for neonates secondary objective was to look at the risk factors associated with AKI and that the Acute kidney injury in the first two weeks of life is associated with increased mortality in Very Low birth infants.
Method. This was a retrospective descriptive study of Very Low Birth Weight infants (<1500) infants admitted in Neonatal Intensive Care Unit at the Universitas Academic Hospital. This study included 58 patients that fulfilled the inclusion criteria and other patients were excluded. Patients' data were obtained through files, Medical records (Meditech) and National Laboratory health services. KIDGO (Kidney disease improving global outcomes) guidelines was used to make the diagnoses of Acute kidney Injury. Results were then classified as Early and Late onset Acute kidney injury and creatine categorized to look at the outcome. Ethical approval was obtained from Health Sciences Ethic committee: Faculty of Health sciences of the University of Free state.
Results. The overall incidence of Acute kidney injury was noted to be 8.6 %(n=7). The incidence of AKI in the early onset Acute Kidney injury group were 6.9 % (n=4) as compared to lower rates of 5.2% (n=3) in the late onset Acute kidney injury group. The most common risk factors for Acute kidney injury was noted to be Sepsis, drug exposure, Perinatal asphyxia and Respiratory distress syndrome. Suspected Sepsis being the highest at 80%. There was a 14.28% (n=1) mortality rate amongst those who had Neonatal Acute kidney injury.
Conclusion. Neonatal AKI is common among VLBW infants in our setting corresponding to other single Centre studies in developed countries. However, we could not establish a relationship between Acute kidney injury and in hospital increased mortality. Risk of Acute kidney injury among infants diagnosed with suspected sepsis was higher compared to those without suspicion of sepsis.

Key words: Acute kidney injury; Creatinine; Risk factors; Kidney disease improving global outcome

LIST OF ABREVIATIONS

ACEI	Angiotensin Converting enzyme Inhibitors
AKI	Acute Kidney Injury
AKIN	Acute Kidney Injury network
CO	Cardiac Output
COX	Cyclooxygenase
ECMO	Extracorporeal Membrane Oxygenation
ELBW	Extreme Low Birth Weight
KIDGO	Kidney Disease Improving Global Outcome
NICU	Neonatal intensive care
NHC	Neonatal High care
PDA	Patent ductus arteriosus
RIFLE	Risk Injury Failure Loss and End stage Renal Failure
RF	Renal Failure
SCR	Serum Creatinine
UAH	Universitas Academic Hospital
VLBW	Very Low Birth Weight

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CHAPTER 1

INTRODUCTION

1.1 BACKGROUND

Acute kidney injury (AKI) previously known as acute Renal failure in neonates is a very common problem in the newborn period. Neonates who are born less than 1500g (namely very low birth weight infants) are at highest risk of developing AKI.[1] Several factors make Premature neonates, especially those that are born with Very Low Birth Weight, more susceptible to AKI than older infants or children. These factors include; developmental immaturity of the renal system kidney, hemodynamic changes that occur at birth and in the early neonatal period that affect the kidney and an increased risk of hypovolemia because of large insensible water losses.[2]

AKI is associated with increased morbidity and mortality amongst patients especially VLBW infants and plays as an independent risk factor for poor outcome.[3] Incidence of AKI depends on the AKI definition used.

The Neonatal kidney collaborative was formed in 2014 to improve the understanding of neonatal Acute Kidney Injury (AKI) and beginning to answer critical questions and improving outcomes in vulnerable populations.[4]

Early recognition of AKI by identifying high risk infants is key to improve the complications and outcome of AKI. This study focuses on identifying the most common risk factors for AKI in neonates.

This study will also determine the morbidity and mortality of those diagnosed with acute kidney injury. Recommendations will then be made, focusing on the identified prenatal, intrapartum and postnatal risk factors, on strategies to decrease the burden associated with

AKI. We define the high-risk category as that of neonates who have the following risk factors: Sepsis, very low birth weight, post-cardiac surgery and patent ductus arteriosus, etc.

CHAPTER 2

LITERATURE REVIEW

There is little data available to support this study in sub Saharan Africa, especially South Africa.

2.1 DEFINITION OF ACUTE KIDNEY INJURY AND DIFFICULTIES IN INTERPRETATION OF SERUM CREATININE VALUES.

Acute kidney injury is defined by David *et al.*, as the decline in renal function, resulting in derangements in fluid balance, electrolytes and waste products.[4] The definition of AKI has evolved over the years depending on the classification used, initially (in 2002) the RIFLE (Risk, Injury, Failure, Loss and end-stage) was used, then AKIN (Acute kidney injury network) in 2007. In 2012 both definitions were combined to formulate a new definition called Kidney Disease Improving Global Outcome (KDIGO) which is currently in use.[1]

Difficulty arise when serum creatinine needs to be interpreted to define AKI.

Table 2.1: Proposed neonatal Aki classification[2]

Stage	SCr	Urine output
0	No change in SCr or increase <0.3 mg/dL	≥0.5 mL/kg/h
1	SCr increase ≥0.3 mg/dL within 48 h or SCr increase ≥1.5-1.9 x reference SCr[a] within 7 d	≥0.5 mL/kg/h for 6-12 h
2	SCr increase ≥ 2-2.9 x reference SCr[a]	<0.5 mL/kg/h for ≥12h
3	Scr increase ≥3 x reference SCr[a] or SCr increase ≥2.5 mg/dL or Receipt of dialysis	<0.3 mL/kg/h for ≥24h or anuria for ≥12h

[a] Baseline SCr is defined as the lowest previous SCr value.

Modified from Jetton JG, Askenazi DJ. Update on acute kidney injury in the neonate. CurrOpin Pediatr 2012;24(2):191-6.

It is noted to be challenging to make the diagnosis in the neonatal period as markers used to make the diagnosis (creatinine and urine output) are signs of renal function and not necessarily damage. Creatinine is also noted to be of maternal origin especially in the first 24-hours of life.[6] The creatinine marker rises as a delayed (48-72 hours) response post a significant kidney damage.[4]

Although both serum creatinine and urine output have limitations, they remain the standard for identifying AKI in critically ill neonates. Immature kidneys and natural physiology of the newborn kidneys makes it difficult to interpret when assessing for AKI. Bruel and colleagues reported critical creatinine levels based on gestational age as a predictor for increased mortality and worse neuro-developmental outcome at two-years of age.[7]

Table 2.2: Creatinine and urine output

Gestational age	Creatinine levels
24-27 weeks	141 mmol/l(1.6 mg/dl)
28-29	97 mmol/l (1.1 mg/dl)
30-32	88 mmol/l(1 mg/dl)

Proposed definitions, validation of the above study and its ability to predict clinical short term and long-term outcomes is very critical for developing a reliable definition of neonatal AKI.

2.2 NEW BIOMARKERS

New Biomarkers have been investigated that give an indication of kidney injury earlier than use of the serum Creatinine as a marker of kidney injury. There are a number of biomarkers but the ones that are promising are: Serum and urinary neutrophil Gelatase ass lipocalin (NGAL), Urinary interleukin 18 (IL 18), Kidney injury molecule (KIM 1), Angiotensinogen, B-2 microglobulin, serum cystatin C.[6] However, this is not the focus of this study.

2.3 RISK FACTORS FOR DEVELOPING AKI

2.3.1 Sepsis

Selewski *et al.* found that sepsis is a significant cause of morbidity and mortality in neonates with AKI and has been identified in neonates making 78% of cases in published literature statistics.[4] Furthermore it is unclear wether the 78% refer to mortality or morbidity.

According to a Thailand's study by Vanvanichsanong *et al.* sepsis-induced AKI had nearly 14 times the risk of death compared to patients with hypovolemia-induced AKI. Sepsis was found to be the most common cause of AKI in their unit. They also noted that sepsis with AKI had a higher mortality rate of about 40-56% for newborns with AKI related sepsis.[8]

2.3.2 Drugs: Maternal and neonatal

Maternal Drugs

2.3.2.1 *Indomethacin*

In pregnancy the use of indomethacin as a tocolytic or pain killer adversely affects the unborn baby as it reduces renal blood flow and glomerular filtration rate (GFR). Nonsteroidal anti-inflammatory drugs (NSAIDs) predispose neonates to a reduction of their renal output and causes AKI.[4]

2.3.2.2 *Anti-hypertensives*

The use of antihypertensive angiotensin converting enzyme (ACE) inhibitor (captopril and enalapril) blocks angiotensin 2, which is kidney protective by maintaining GFR. There's also a risk of renal agenesis to AKI.[4]

2.3.3 Neonatal

Drugs such as Amphotericin B, Aminoglycosides, and ACE inhibitors are nephrotoxic as they cause vasoconstriction of the renal vessels which leads to decreased blood flow through the kidneys.

Based on the study by Akima *et al.* (2004), 24% of 54 newborns with gestational age <30 weeks and receiving indomethacin for PDA closure developed AKI.[9] This is a prevalence which is similar to a study done in Thailand; where 10 out of 41 neonates were diagnosed at gestational age <32 weeks.[8]

2.3.4 Birth weight: VLBW and ELBW neonates

Studies done in this group looked at weight categories from 500g to 1500g. According to Koralkar *et al.* (2011) a large study that looked at 229 very low birth weight, had incidence of 18% using the KDIGO classification but the mortality was noted to be higher (about 2.4 increased rate) if patient had AKI.[10]

Viswanathan *et al.* reported 12.5% in ELBW (Birth weight of less than 1000g), with higher mortality rates.[11]

2.3.5 Asphyxia

Kaur *et al.* reported 41.7% incidence of AKI[12] and Selewski *et al.* reported that 38% of 96 cases had AKI in neonates who had undergone therapeutic hypothermia.[13]

Vanvanichsanong *et al*. (2011) completed a study which took 24 years that reports asphyxia as the most common risk factor contributing to AKI at 40.0%, followed by sepsis/metabolic disease (22.2%) and feeding problems (17.8%).[14]

2.3.6 Extracorporeal membrane oxygenation (ECMO)

The use of ECMO increases the risk of AKI in neonates merely because of the inflammatory response to the exposure to extracorporeal circuit. Zwiers *et al.* performed a study looking at AKI in 242 neonates on ECMO over a 14-year period: 64 % had AKI and 65% were mortality cases when AKI progressed to end stage kidney disease.[15]

2.3.7 Neonatal cardiac surgery

Multiple studies have been done to prove the association between AKI and cardiac surgery in children. Alabbas *et al.*, performed a retrospective study where they looked at 122 neonates less than 28 days old and 62% had AKI. The neonates with the end stage of AKI was associated with mortality and increased length of stay in ICU.[16]

CHAPTER 3

INTRODUCTION

Acute kidney injury in very low birth weight neonates has been identified but under reported especially in South Africa. Neonates who are born very premature are at increased risk of AKI as a result of immature kidney and several potential exposures (e.g. Nephrotoxic drugs, sepsis, hypotension, adverse perinatal events such as asphyxia). The main objective of this study is to measure the incidence, identify risk factors and look at the outcomes of AKI in our neonatal Unit.

We could not find studies regarding incidence of AKI amongst Neonates and very low birth weight in the South-African setting. Certainly, records on this subject is not available in Universities academic hospital. The under reporting of these incidences makes it difficult for the management and follow up plans especially in the public health sector.

To determine the relevant causative risk-factor for AKI in neonates at the Universitas Academic Hospital, we looked at the following for information:

- Blood results specifically Creatinine from National health laboratories services;
- Patients files were used to look at maternal and neonatal risk factors;
- Meditech system to supplement files and other information needed to complete the study.

Data was then collected retrospectively as a snap shot for a period of six months. The information was then used to classify those who had AKI according to Kidney Disease Improving global outcomes. However, urine output was not used to define AKI.

We enrolled all patients who were admitted in the six-month period as very low birth weight neonate in NICU. There are several Etiological risk-factors identified for AKI in neonates. We have looked at the following:

- Neonatal risk factors: Sepsis, Asphyxia, drugs, birth weight, ECMO, respiratory distress syndrome, birth weights, gestational ages and cardiac surgery.

- The Maternal risk factors: Pregnancy induced hypertension, drugs, infection and nonsteroidal anti-inflammatory drugs.

The most common risk factor for AKI proves to be sepsis even in the developed world ranging from 2-40% by Nillsen, 2016, these studies were done from 2011 to 2016.[17] The incidence of sepsis was noted to be higher in our study. This also then puts all our patients at risk for receiving aminoglycosides which adds to the burden of disease. Other risk factors that are of significance is Perinatal asphyxia at 11.5 % reported by Vanvanichsanong *et al*. further noted that the incidence can be as high as 40-56% as per other studies.[8] Other risk factors were also investigated to complete the study.

Looking closely at the outcomes especially mortality; we did find an association between the AKI and mortality as those who had AKI had 14% mortality rate. The mortality rate ranges from 4.5-78 % as noted by Vesna Stojanovic *et al.* (2014).[18] It is of significant importance to note similarity in our study as compared to the developed world.

In conclusion we were able to Prove that our Incidence of AKI was quiet similar to the study done by Charlton, J.R. *et al.*, an AWAKEN study (Assessment of worldwide Acute kidney injury epidemiology in neonates).[19] This has also proved the mortality rate to be 14.2% in keeping with international data.

CHAPTER 4

RESEARCH METHODS AND DESIGN

4.1 RESEARCH METHODS AND DESIGN

An Observational, Retrospective, Descriptive study was conducted on patients that were admitted in the Universitas Academic Hospital, which is a Tertiary Hospital in the Free State. The population selected for our study was Very Low Birth Weight, i.e. weight less than 1500 g, (VLBW) infants in their first two weeks of life, admitted at the Universitas Academic Hospital, Neonatal unit, from January-June 2016.

4.1.1 Data collection

Data was collected from patients' files and electronic data capturing system (discharge summaries) and National Health Laboratory services (NHLS). In the patients' files and Meditech system, we have gathered the following information: Maternal and neonatal risk factors as well as the possible outcomes. Also, urine output was analyzed but not quantified and therefore did not form part of the KDIGO definition of AKI in our study.

At the NHLS we looked at all creatinine done especially in the first two weeks of life. All bloods taken on Day 1, 2, 3, 6/7, 13/14 blood results were captured. All these were patients that were admitted from January-June 2016 in Neonatal ICU. An excel spreadsheet was used to enter all qualifying neonates and all relevant variables were entered.

Our study then captured 68 patients, some were excluded as per our exclusion criteria. This number has given us a snapshot over the specified time frame. This sample size was acceptable and was able to fulfil the objectives of the study.

4.1.2 The KDIGO guidelines[5] :

- STAGE 0: No change in creatinine or the increase is <0.3mg/dl
- STAGE 1: Increase in Serum Creatinine by >/= to 0.3 mg/dl (26.5 mmol /l) within 48 hours; or
- STAGE 2: Increase in Serum Creatinine to >/= 1.5 times baseline, which is known; or
- STAGE 3: Presumed to have occurred within the prior 7 days;

4.2 STASTICAL ANALYSIS PLAN

A data capture sheet was used to record the information. The hospital file number was used anonymously on this form. This is then linked to the study participant name via a coding

sheet. The information on the data capture sheet was then put into an excel spread sheet for further analysis by the Department of Biostatistics.

Every patient admitted was reviewed based on their biochemical results and evaluated according to the inclusion and exclusion criteria. Infants were classified as having AKI if they met the serum creatinine definition only according to KDIGO definition. Urine output, which is part of KDIGO method of defining AKI, was not used in this study for various reasons. A reliable and quantifiable urine output for more than 24-hours during the study period amongst selected study group was scarcely obtained.

We looked at the creatinine values and categorized them into groups looking at the mortality rates as well as the incidence of AKI in those specific categories. These categories also enable us to identify those at risk for AKI based on the trends in creatinine values.

4.2.1 Inclusion criteria

Neonates with birth weight of 1500 g or including extremely low birth weight infants in their 30 days of life, VLBW babies who have had base line bloods, renal function (urea and electrolytes) in their first 24-48 hours and a repeat of at least two renal function bloods done at least 24-hours apart and bloods should have been taken at least on day 7 and or day 14.

4.2.2 Exclusion criteria

Neonates that are more than 1500 g in weight. Patients that are older than 30 days on admission; Patients who demise within 48-72 hours of life; any patient with chromosomal abnormalities and Patients admitted in neonatal high care as they had no adequate sample of bloods taken to meet the inclusion criteria

4.3 ETHICAL CONSIDERATIONS

There were no participants consent forms required for this study as anonymous archival data was used. The research protocol was submitted and approved by the Human Research Ethics Committee of the University of Free State (ref. no: UFS-HSD2017/1553/2509). Permission was obtained by the Head of Department of Pediatrics at the Universitas Academic Hospital, Head of Neonatology.

CHAPTER 5

RESULTS

5.1 RESULTS AND FINDINGS

Figure 5.1 is a flow diagram showing all patients included and excluded in our study.

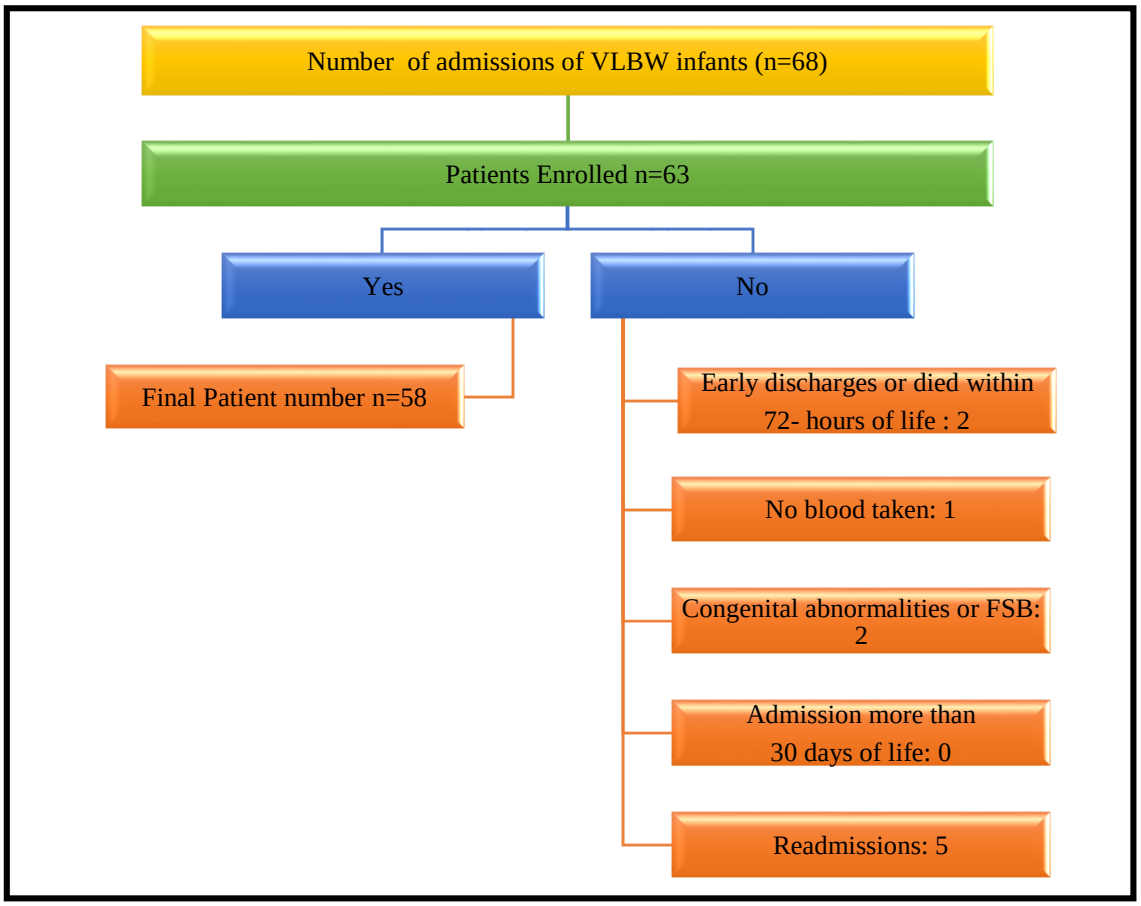


Figure 5.1: Patients included and excluded

We enrolled 68 infants who were less that 1500g admitted in NICU in the 6-month period. All 58 patients (85%) could fulfill the inclusion criteria and 10 were excluded as per Figure 5.1. These patients were noted to be of gestational age (GA) less than 34 weeks. The mean gestational age was 29 weeks with birth weight of 1100g. The minimum GA was 26 weeks with maximum being 34 weeks. Only one had fewer than two serum creatinine and two demised within the first 48-hours. Frequency of serum creatinine measurements reflect local standard of care at the time of the study. AKI events occurred during the second week after birth.

5.2 RELATIONSHIP BETWEEN RISK FACTORS AND ACUTE KIDNEY INJURY

Table 5.1 Tabulates variables used to diagnose acute kidney injury.

Variable	AKI	No AKI	Percentage
Weight			
< 1000 g	1	12	
1000 – 1500 g	6	41	
Gestational age 26-			
<28 weeks	0	12	
28- <30 weeks	4	23	
30- <32 weeks	1	15	
32- <34 weeks	0	3	
Apgars			
≤5 at 5min	0	9	
>5 at 5 min	5	44	
RDS	4	35	
Sepsis	4	46	
Drugs	5	53	

5.2.1 Sepsis

All neonates were screened for sepsis at birth. The incidence of suspected neonatal sepsis was noted to be 80%. No cultures were taken at birth to prove sepsis. Every patient with a raised CRP /deranged white cells were treated for sepsis. However, in the late onset sepsis bloods cultures were taken but was not part of the study.

5.2.2 Aminoglycoside

As we Considered the high rates of sepsis in our unit. All babies were given aminoglycosides: Amikacin and vancomycin formed part of the second line antibiotic therapy.

5.2.3 NSAIDS

No reports of NSAIDS used in all our patients.

5.2 Maternal hypertension

The incidence of pregnancy-induced hypertension was not part of our study. We looked at the incidence of babies born from mothers with PIH as a risk factor which and was noted to be 80%. We however could not identify the type of medication taken during pregnancy.

5.2.5 Respiratory distress syndrome

Very low birth infants especially in those less than 34 weeks of life are susceptible to develop Respiratory distress syndrome. We diagnosed 60% of patients with RDS.

5.2.6 Asphyxia

The incidence of asphyxia was noted to be only 20 % in our unit. We looked at all Apgar's at five-minutes, as well as other qualifying criteria for perinatal asphyxia.

5.2.7 ECMO

We do not have an ECMO machine to prove ECMO as a risk factor.

5.2.8 Cardiac surgery

No patient was sent for cardiac surgery.

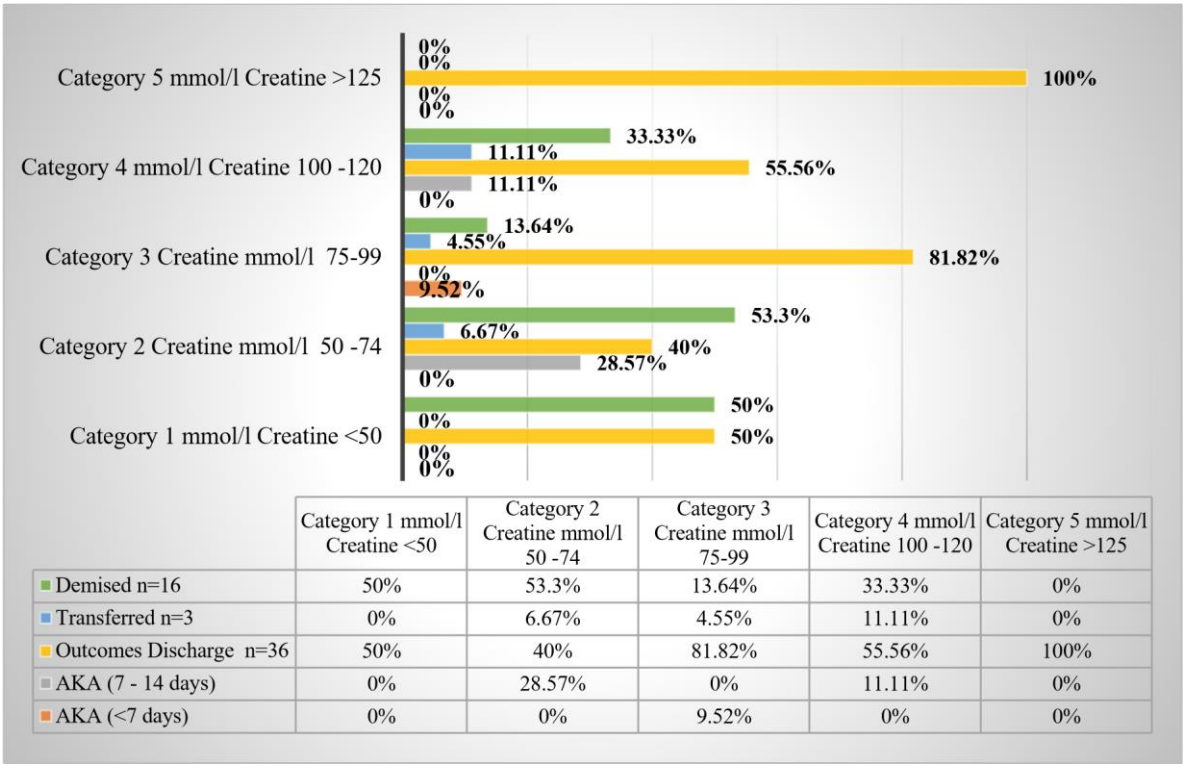
5.3 ACUTE KIDNEY INJURY INCIDENCE

We have looked at incidence in two different scenarios: Early onset AKI as defined by a patient less than seven days of life and late onset AKI as defined by 8-14 days of life. The total incidence of AKI in our study was 12.1% (n=7). It was further noted that the incidence of early and late AKI was 6.9% (n=4) and 5.2% (n=3).

5.4 SEVERITY OF ACUTE KIDNEY INJURY

There were only 1.72 % and 6.9 % respectively for stage 1 and stage 2 AKI according to KIDGO. There was 87.9% who had no AKI.

AKI and outcomes:



	Category 1 mmol/l Creatine <50	Category 2 Creatine mmol/l 50 -74	Category 3 Creatine mmol/l 75-99	Category 4 mmol/l Creatine 100 -120	Category 5 mmol/l Creatine >125
Demised n=16	50%	53.3%	13.64%	33.33%	0%
Transferred n=3	0%	6.67%	4.55%	11.11%	0%
Outcomes Discharge n=36	50%	40%	81.82%	55.56%	100%
AKA (7 - 14 days)	0%	28.57%	0%	11.11%	0%
AKA (<7 days)	0%	0%	9.52%	0%	0%

Figure 5.2: Relationship graph between AKI and Mortality

The above graph notes the relationship between AKI and Mortality. As noted above AKI was noted to be more common in the Category 2 group (Cr: 50-74) with 28.57% of AKI in the second week of life. In the same group it was noted that 50% of Patients died. Of note the Category 5 patients had no deaths nor AKI and they were all discharged home.

5.5 STATISTICAL ANALYSIS

Continuous variables were summarized by medians, minimum or percentiles. Categorical variables like (incidence of AKI and morbidity/mortality) was summarized by frequencies and percentages. Associations between categorical variables were evaluated using appropriate statistical tests. The Fisher exact test was used. The analysis was done by the Department of Biostatistics, using statistical Analyses Software (SAS9.4)

CHAPTER 6

DISCUSSION

6.1 DEMOGRAPHIC

As noted in table 5.1, the GA ranges between 26-34 weeks of life. This is statistically important as the kidney fully matures at 34 -36 weeks of gestation. (4) .They were 80 % of patients who has AKI that were born between 28-30 weeks; this is possible owing to immature kidney and risk factors exposed to. Surprisingly 80% of our babies have AKI and are VLBW (1000g-1500g) babies. In comparison to the international standards, these percentages seem to be similar but lower in a sense that Arcinue *et al*., had 26 % prevalence in a 10 year study and found an association with higher mortality rates.[20]

6.2 INCIDENCE

The Incidence of AKI depends on many factors including the AKI definition used. We use the KIDGO guidelines to define AKI in this study. The total incidence of AKI in this study is noted to be 12.1 % and is further subdivided in to Early onset AKI at 6.9% and late at 5.2 % the late onset AKI.

Previous research noted the incidence to range between 18-40 %.[21] In 2011, Koralkar *et al.* conducted a study in VLBW neonates with n=229. The incidence was then noted to be 18 % by using the KDIGO guidelines.[10] Vesna *et al.* further classifies the AKI into non oliguric and oliguric AKI. The common type of AKI in neonates is non-oliguric at 60% and oliguric at 25 % or anuric at 15%.[18] We however did not look at the different types of AKI as urine output did not form part of AKI definition. As The incidence of overall incidence of AKI is 12.1% in this study ,this is interpreted as remakarbly low as compared to the international stardards. bearing in mind that this results needs to be further subdivided in to early and late. The results concur with the AWAKEN study conducted in n=2152.[19] Our results are however lower than their results when comparing the early onset neonatal kidney injury. This could be explained by few factors including small sample size, urine output was not included as AKI definition and a few serum Creatinine measurements taken as a reflection of standard of care at the time.

Staging of AKI places, the patients in different categories with increased risk factors for mortality and chronic renal failure. Fortunately, there was no patient who had stage 3 AKI. Studies done by Koralkar and Askinazie which proved higher mortality rates of 4.8-56.7 % and 19.1 % respectively.[18] The 6.9 % percentage incidence of early onset AKI warrants us to look closely on maternal risk factors and mobility associated with it.

6.3 RISK FACTORS

Early onset AKI is associated mainly with maternal risk factors whereas late onset AKI is associated with Neonatal risk factors. The most common risk factor causing AKI in our study remains sepsis at 80 %. It is of note that this sepsis is not proven (no positive cultures) but suspected. Nillsen *et al*. (2016) conducted a study looking at various studies done from 2011 to 2016.The incidence of confirmed neonatal sepsis was noted to be between 1.57 % to 41%.[22] Maybe the incidence in our study could have been different had we focused on AKI with confirmed sepsis. These higher rates of sepsis then have placed all patients in receiving aminoglycoside at birth therefore contributing to many problems related to aminoglycoside exposure. However, routine Aminoglycoside levels were done on day three of drug use. We did not follow up on the results as this did not form part of our study.

Neonates diagnosed with Asphyxia were 20% which is below the Kaur *et al.* (2011) at 41.7 %[12] and Selekwi *et al.* at 38 %.[13] Respiratory distress syndrome is mainly the main reason for admission in NICU. The AKI rate in these patients were noted to be 71% which is statically significant in 2018. Azar *et al.* noted the higher risk of AKI in RDS patients. This was noted to be lower at 26%.[23] **It was of great concern that** 72% of the study population had RDS, which could be explained by low number of mother with preterm deliveries that received antenatal steroids.

There was no note of tocolytics given nor ACE inhibitors given to the mothers. We also noted the association between chorioamnionitis and AKI even though that was not part of the initial variable. Patients that had maternal chorioamnionitis in our study were noted to have AKI, we then recommend further investigation in that regard.

6.4 OUTCOMES

The outcome of AKI in our patients in our study were noted to be as follows: Category 5

(creatinine >125 mmol/l) patients were all discharge followed by Category 3 (75-99 mmol/l)

with 81.8 % rate. This is surprising results as we did not expect Category 5 patient not to have AKI and nor mortality. Bruel *et al.*, looked at critical creatinine levels based on gestational age[7] and therefore we were expecting higher mortality rates especially in Category 5 patients. The highest mortality rate was noted to be 53.3 % in the Category 2 (50-74 mmol/l) followed by Category 1 (<50 mmol/l) patients. Few Inferences can be made namely that isolated high serum creatinine is poor predictor of increased mortality and shortterm outcome.

Serum creatinine and urine output remain the standard for identifying AKI events in critically ill infants, although both have limitations. It is of significantly importance to note that 11.11 % patients were transferred to local hospitals for further care. We do not know whether they died or stayed longer there, although majority of hospitals refer to us if they get seriously ill during hospital stay. A robust, prospective collected data on long-term outcome (Especially chronic kidney disease) following neonatal AKI needs to be done.

6.5 STRENGTH OF THE STUDY

One of the few studies which attempted to look at incidence of AKI and therefore highlighting that high index of suspicion is warranted. Highlighted the fact that the true incidence of AKI in preterm population is difficult to establish as the preterm infants has immature tubular function. Therefore, serum creatinine-based definitions of AKI are perhaps ill suited for this group.

6.6 LIMITATIONS OF STUDY

Retrospective study and we had to rely on serum creatinine data available in the medical records. Therefore, AKI cases could have being missed. We acknowledge that quantification on urine output is important of assessment of AKI. Because of few reasons, namely retrospective type of study, difficult in placement of urinary catheter in preterm infants and risk of catheter-associated infection. Maternal co-founders were difficult to obtain because of poor obstetric care during the time of study in our province.

There are many variables that have not been looked at for example: Ventilation, PDA, length of stay, maternal risk factors that could have played a role in the development of AKI in our patients but never documented as such. The next study could explore more on those variables

in addition to the work done[2]. The exclusion of urine output as nappies were not weighed nor urine catheters inserted.

6.7 CONCLUSION

AKI is common amongst preterm infants (VLBW & ELBW) in developing countries like the developed world. Sepsis and Asphyxia still leads as the causative variable in the VLBW infants.

The incidence of AKI is 12,1% is remarkably low in comparison with the literature .It is almost equally distributed between early 6.9% (n=4) and late 5.2% (n=3) onset with the early onset group being slightly bigger.

Larger multicenter prospective studies are needed to establish a relationship between AKI and increased mortality. Development of novel AKI definition based on urine and serum biomarkers concentrations are required since serum creatinine/Urine output definitions are suboptimal in preterm population.

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APPENDICES

APPENDIX A: APPROVAL LETTER FROM ETHICS

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

31-Aug-2018

Dear **Dr Princess Ngwenyama**

Ethics Clearance: **THE INCIDENCE OF ACUTE KIDNEY INJURY AMONGST VERY LOW BIRTH WEIGHT NEONATES IN THE NEONATAL UNIT AT UNIVERSITAS ACADEMIC HOSPITAL DURING THE PERIOD OF JANUARY 2016 TO JUNE 2016**

Principal Investigator: **Dr Princess Ngwenyama**

Department: **Paediatrics and Child Health Department (Bloemfontein Campus)**

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is: **UFS-HSD2017/1553/2509**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
IRB 00006240; REC 230408-011; IORG0005187; FWA00012784

APPENDIX B:

APPROVAL LETTER FROM THE DEPARTMENT OF HEALTH

health
Department of Health
FREE STATE PROVINCE

27 August 2018

Dr. P Ngwenyama
Dept. of Peadiatrics and Child Health
UFS

Dear Dr. P Ngwenyama

Subject: The incidence of Acute kidney injury among very low birth weight neonates in the neonatal unit at Universitas Academic Hospital during the period January 2016 to June 2016

- Please ensure that you read the whole document, Permission is hereby granted for the above – mentioned research on the following conditions:
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of Universitas Academic Hospital nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** lithekom@fshealth.gov.za or sebeelats@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- Please discuss your study with the institution manager/CEOs on commencement for logistical arrangements
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- You are encouraged to present your study findings/results at the Free State Provincial health research day
- Future research will only be granted permission if correct procedures are followed see http://nhrd.hst.org.za

Trust you find the above in order.
Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 30/8/18

Head : Health
PO Box 227, Bloemfotein, 9300
4th Floor, Executive Suite, Bophelo House, cnr Maitland and, Harvey Road, Bloemfotein
Tel: (051) 408 1646 Fax: (051) 408 1556 e-mail:khusemj@fshealth.gov.za@fshealth.gov.za/chikobvup@fshealth.gov.za

APPENDIX C: PERMISSION FROM HEAD OF DEPARTMENT;UAH NEONATL UNIT

Universitas Academic /Tertiary Hospitals

Neonatal ICU and High care unit

9th December 2019

Head/ Acting Head

Department of Paediatrics and Child Health

University of the Free State

Re: Permission to conduct a Retrospective observational study by our registrar

Subject: **THE INCIDENCE OF ACUTE KIDNEY INJURY AMONGST VERY LOW BIRTH WEIGHT NEONATES IN THE NEONATAL UNIT AT UNIVERSITAS ACADEMIC HOSPITAL DURING THE PERIOD OF JANUARY 2016 TO JUNE 016**

CANDIDATE: DR ZP NGWENYAMA

I hereby, wish to confirm that I did give the above-mentioned registrar the permission to do a MMed study in our NEONATAL CARE UNIT at Universitas Hospital subject to approval of her protocol by Universitas Management and University of the Free State.

The study is also beneficial for both quality improvement and better patient care.

Kind regards

Dr TB Mosia

Head of Clinical Unit, Neonatology

Signature

Stamp

APPENDIX D: LETTER OF APPROVAL FROM THE NHLS

NATIONAL HEALTH LABORATORY SERVICE

Practice No. 5200296

Office of the Business Manager
UNIVERSITAS ACADEMIC LABORATORIES
PO BOX 339(G3)
C/O: CHEMICAL PATHOLOGY
1ST FLOOR
BLOCK C
FACULTY OF HEALTH SCIENCES
UNIVERSITY OF FREE STATE
BLOEMFONTEIN
9301

REQUEST FOR APPROVAL OF LABORATORY RESOURCES FOR ACADEMIC PURPOSES

Date: 10 December 2019

Requestor: Dr PZ Ngwenyama

Project Name: "THE INCIDENCE OF ACUTE KIDNEY INJURY AMONGST VERY LOW BIRTH WEIGHT NEONATES IN THE NEONATAL UNIT AT UNIVERSITAS ACADEMIC HOSPITAL DURING THE PERIOD OF JANUARY 2016 TO JUNE 2016."

Dear Dr PZ Ngwenyana,

Your request for use of laboratory facilities / data is hereby granted under following conditions:

1) That University Ethical Committee approval and approval from the Universitas Hospital management is obtained
2) All laboratory data remain confidential to the patient and doctor (anonymity is maintained)
3) This Office must be notified before any publication of any results / findings are made.
4) NHLS is recognised in all publications
5) That a successful K-Project application be made and relevant NHLS project cost centre be created to utilise testing at NHLS as per your protocol.

May your project be successful.

Regards

NATIONAL HEALTH LABORATORY SERVICE
Acting 10 DEC 2019
BUSINESS MANAGER
UNIVERSITAS ACADEMIC LABORATORIES

Mr. Pakiso Letanta
Acting Business Manager

APPENDIX E:

TURN-IT-IN REPOR

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APPENDIX F: DATA COLLECTION SHEET

Pnumber	Weight		DOA YEAR	DOA Month	DOA DAY	GA	Creatinine				Urinary output			Sepsis	Aminoglyc	Maternal risk factors		RDS	ASPHYXIA	Ecmo	CARD SURG	AKI	outcome	Gender	GRADE
		DOA					D1	D2	D3	7 d 7	d14	D2	D3		YES/NO	NSAIDS	ANTIHPT	yes/NO	YES/NO			yes/NO			
																	YES/NO								
699672	1020	06-05-201	62016	5	6	28	93	96	81	48	40			y	y	N	y	y	Y	N	N	N/N	DC	M	0
698990	1200	24-4-2016	2016	4	24	31	80	75		62	33			Y	Y	N	N	N	N	N	N	N/N	DC	M	0
699443	1310	05-3-2016	2016	3	5	29	77	84	65		57			Y	Y	N	Y	Y	N	N	N	N/N	DC	F	0
701254	1100	16-05-201	62016	5	16	28	82	25	62	43				Y	Y	N	N	Y	N	N	N	N/N	DC	F	0
700816	1230	21-05-201	62016	5	21	29	76	98	80	80	68			Y	Y	N	Y	Y	N	N	N	N/N	DC	F	0
698000	1090	21-05-201	62016	3	4	27		96	95	88	83			Y	Y	N	Y	Y	N	N	N	N/N	DC	M	0
702484	1010	16-06-201	62016	6	16	26			68	47	48			Y	Y	N	N	Y	N	N	N	N/N	DC	F	0
702485	890	16-06-201	62016	6	16	26			60	58	57			Y	Y	N	N	Y	Y	N	N	N/N	DC	F	0
691837	1001	03-01-201	62016	1	3	28		97	79	32	35			Y	Y	N	Y	Y	Y	N	N	N/N	DC	F	0
691805201	1080	01-01-201	62016	1	1	28	54	95	86	80	77			Y	Y	N	N	Y		N	N	N	yes/NO	DC	M	1
692103	810	08-01-201	62016	1	8	28	65	77	58	30	54			Y	Y	N	N	Y	N	N	N	N/N	DC	F	0
692342	900	12-01-201	62016	1	12	28				81	53			Y	Y	N	N	Y	N	N	N	N/N	T	F	0
692341	1470	12-01-201	62016	1	12	32				157	67			Y	Y	N	N	N	N	N	N	N/N	DC	F	0
691663	910	13-01-201	62016	1	13	30	102	98	51	36	32			Y	Y	N	Y	Y	N	N	N	N/N	D	M	0
692412	800	13-01-201	62016	1	13	31	86	108	101	54	61			N	Y	N	Y	N	Y	N	N	N/N	T	F	0
									E	X	C	L	U	D	E	D									
692834	1050	20-01-201	62016	1	20	35	76	86	50	25	18			N	Y	N	Y	N	N	N	N	N/N	DC	M	0

693016	870	25-01-201	6201 6	1	25	27	48	69	52	33	69			N	Y	Y	Y	Y		Y	N		N	N/YES	DC	F	1
693305	1300	27-01-201	6201 6	1	27	32	81	40	46	43	52			Y	Y		N	N	Y	N		N	N	N/N	DC	F	0
693991	1010	27-1-2016	6201 6	12	2710	28	113	110	78	30	36			Y	N	Y	N	Y		N		N	N	N/N	D	F	0
693894	1010	10-02-201	6201 6			27	46	49	34	46	49			N	Y	N	Y	N		N		N	N	N/N	DC	F	0
691805	1080	10-02-201	6201 6	2	10	28	54	95	86	79	70	CHORIO		Y	Y	N	N	Y		N		N	N	YES/NO	DC	M	1
694669	930	15-02-201	6201 6	2	15	29		103	92	45	55			Y	Y	N	Y	Y		N		N	N	N/N	DC	F	0
694879	1410	18-02-201	6201 6	2	18	31	113	79	58	56	43			N	Y	N	Y	Y		Y		N	N	N/N	DC	F	0
695060	1070	21-02-201	6201 6	2	21	31				38	66			Y	Y	N	N	N		Y		N	N	N/YES	D	F	1
695990	1130	05-03-201	6201 6			32	80	87	69	47	43			Y	Y	N	Y	Y		N		N	N	N/N	TF	F	0
696429	1400	11-03-201	6201 6	33	511	31	130	111		56	44			Y	Y	N	Y	N		N		N	N	N/N	DC	M	0
696804	1400	16-03-201	6201 6	3	16	30			61	38	22			Y	Y	N	Y	Y		N		N	N	N/N	DC	F	0
696810	1430	16-03-201	6201 6	3	16	30	97	52	38	46				N	Y	N	N	Y		N		N	N	N/U	DC	F	0
696916	1200	17-03-201	6201 6	3	17	31	118	84	84	53	46			N	Y	N	Y	Y		N		N	N	N/N	D	M	0
697244	1110	27-03-201	6201 6	3	27	29	91	92	82		none			Y	Y	N	Y	Y		N		N	N	N/N	D	M	0
697258	1000	28-03-201	6201 6	3	28	29	156	116	92	54	45			N	Y	N	Y	Y		Y		N	N	N/N	DC	M	0
697219	1150	25-03-201	6201 6	344	251010	32	76		62	62				N	Y	N	Y	N		N		N	N	N/N	DC	F	0
698053	920	10-04-201	6201 6			27	62	64	77	60	none			Y	Y	N	N	Y		Y		N	N	N	D	F	0
698052	920	10-04-201	6201 6			27	66	68	72	70	none			Y	Y	N	Y	Y		N		N	N	N	D	F	0
								E		X		C		L		U		D		E		D			0
702198	1350	11-06-201	6201 6	6	11	30			254	35	21			Y	Y	N	Y	Y		N		N	N	N	DC	F	0
698551	1030	17-04-201	6201 6	4	17	27	127	125	106	50	32	ATN		Y	Y	N	Y	Y		N		N	N	N	DC	F	0
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698818	1160	20-04-201	6201 6	4	20	28				37	18			Y	Y	N	U	N	N	N	N	N	D	M	0
698992	1010	24-04-201	6201 6	4	24	26			64	55				Y	Y	N	N	Y	N	N	N	N	D	M	0
698991	880	24-04-201	6201 6	4	24	26	45	47	44	34				Y	Y	N	N	Y	N	N	N	N	D	F	0
698974	1080	24-04-201	6201 6	4	24	28		78	51		38	not marked		Y	Y	N	Y	Y	N	N	N	N	DC	F	0
698054	1170	10-04-201	6201 6	4	10	27		54	54	34	50			Y	Y	N	Y	Y	N	N	N	N	TF	M	0
693016201	1420	03-04-	6201 6	1	24	27	48	69		47	115			Y	Y	N	Y	Y		Y	N	N	N/YES	DC	F	2
699780						E			X			C		L			U			D		E		D			
697019	1260	15-05-201	6201 6	5	15	26		52		60	none			Y	Y	N	N	N	N	N	N	N	D	M	0
701379	1220	30-05-201	6201 6	5	30	30			54	46	43			Y	Y	N	N	Y	N	N	N	N	D	F	0
701538	1180	01-06-201	6201 6	6	1	31	113	111	71	50	32			Y	Y	N	Y	Y	Y	N	N	N	U	M	0
	E		X		L		U		D		E		D													
701891112000		07-06-2016	2016	6	7	29	72		55				38	N	Y	N	Y	N	N	N	N	N	D	F		
702292	1110	13-06-201	5	2016	6	13	27		51	53	58	56			Y	Y	N	Y	N	N	N	N	N	T	M	0
694658	1180	25-02-201	5	2016	6	25	29	104	104	81	73	71			Y	Y	N	Y	Y	N	N	N	N	D	F	0
692100	1230	07-01-201	5	2016	1	7	29	99	93	67	45	none			Y	Y	N	Y	Y	Y	N	N	N	TF	M	0
702486	1280	16-06-201	5	2016	6	16	30		45	43	45	36			Y	Y	N	N	N	N	N	N	N	DC	M	0
699278	1152	28-04-201	5	2016	4	28	29	103	104	78	53	36			Y	Y	N	Y	Y	N	N	N	N/N	D	M	0
702562	880	20-06-201	5	2016	6	20	27			64	59	59			Y	Y	N	N	Y	N	N	N	N/N	D	F	0
703037	890	24-06-201	5	2016	6	24	30	105		79	37	35			Y	Y	N	Y	N	Y	N	N	N/N	DC	F	0
703021	950	24-06-201	5	2016	6	24	29	82	91	71	59	49			Y	Y	N	Y	N	N	N	N	N/N	DC	F	0
702661	1330	20-06-201	5	2016	6	20	31		106	64	50				Y	Y	N	Y	N	N	N	N	N	TF	F	0
703216	1260	28-06-201	5	2016	6	28	29		72	65	61	37			Y	Y	N	Y	Y	N	N	N	N/N	DC	F	0
703219	1260	28-06-201	5	2016	6	28	29	62	70	62					Y	Y	N	Y	Y	N	N	N	N/U	D	F	0

703390	1200	30-05-201	5	2016	5	30	31		87	65	59	53			Y	Y	N	Y	N	N	N	N	N	DC	M	0

COPY OF RESEARCH PROTOCOL APPROVED BY HEALTH SCIENCE RESEARCH ETHICS COMMITTEE

THE INCIDENCE OF ACUTE KIDNEY INJURY AMONGST VERY LOW BIRTH WEIGHT NEONATES IN THE NEONATAL UNIT AT UNIVERSITAS ACADEMIC HOSPITAL DURING THE PERIOD OF JANUARY 2016 TO JUNE 2016

By

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INDEX

TABLE

FIGURE

ABBREVIATION

ACE	**Angiotensin converting enzyme**
AKI	**Acute Kidney Injury**
AKIN	**Acute kidney injury network**
CO	**Cardiac Output**
COX	**Cyclooxygenase**
ECMO	**Extracorporeal membrane oxygenation**

ELBW	**Extreme low birth weight**
GFR	**Glomerular Filtration Rate**
KDIGO	**Kidney disease improving global outcome**
NICU	**Neonatal intensive care unit**
NHC	**Neonatal high care unit**
PDA	**Patent ductus arteriosus**
RIFLE	**Risk, injury, Failure, loss and end stage renal disease**
RF	**Renal Failure**
sCr	**Serum Creatinine**
UAH	**Universitas Academic Hospital**
VLB	**Very low birth weight**

W

Appendixes

Not attached !

THE INCIDENCE OF ACUTE KIDNEY INJURY AMONGST VERY LOW BIRTH WEIGHT NEONATES IN THE NEONATAL UNIT AT UNIVERSITAS ACADEMIC HOSPITAL DURING THE PERIOD OF JANUARY 2016 TO JUNE 2016

1.1 INTRODUCTION

Acute kidney injury (AKI) previously known as acute renal failure in neonates is a very common problem in the newborn period. Neonates who are born less than 1500g (namely very low birth weight infants) are at highest risk of developing AKI. Several factors make premature neonates, especially those that are born with very low birth weight), more susceptible to acute kidney injury than older infants or children. These factors include: Developmental immaturity of the renal system kidney, hemodynamic changes that occur at birth and in the early neonatal period that affect the kidney and also an increased risk of hypovolemia because of large insensible water losses.(1)

Recent data suggest an association between AKI with increased morbidity and mortality amongst patients, therefore AKI can no longer be viewed as an incidental finding. AKI is an independent risk factor for poor outcome in this very low birth weight patient population. The reported incidence of AKI in the neonatal intensive care unit varies widely depending on the parent sampling and AKI definition. In the available literature there are a dozen of definitions of AKI.(2)

The neonatal kidney collaborative was formed in 2014 to improve the understanding of neonatal acute kidney injury (AKI) and beginning to answer critical questions and improving outcomes in vulnerable populations.(3)

The research in this field project is necessary to bring awareness of the most common causes of AKI in neonates. Early recognition of AKI is key to ameliorating the complications of AKI. Early recognition of at risk patients also improves the outcome of these patients.

This study will focus on identifying the most common risk factors for AKI in neonates.

We will also determine the morbidity and mortality of those diagnosed with acute kidney injury. Recommendations will then be made, focusing on the identified prenatal, intrapartum and postnatal risk factors, on strategies to decrease the burden associated with AKI.

The high-risk category is defined as patients who have the following risk factors: sepsis, very low **birth** weight, post cardiac surgery, hypoxia, etc.

1.2 BACKGROUND AND LITERATURE REVIEW

There is little data available to support this study especially in sub Saharan Africa, includingSouthAfrica.

Acute kidney injury which was previously known as acute renal failure, is characterized by sudden rapid decrease in renal function which causes imbalance in electrolytes, acid -base status and excretion of waste products (4). The term "failure" is used for conditions requiring renal replacement therapy, peritoneal or hemodialysis.

Acute kidney injury is defined as the decline in renal function, resulting in derangements in fluid balance, electrolytes and waste products. It is noted to be challenging to make the diagnosis in the neonatal period as markers used to make this diagnosis (creatinine and urine output) are signs of renal function and not necessarily damage. Creatinine is also noted to be of maternal origin especially in the first 24 hours of life(5)[i] The creatinine marker is noted to rise 48-72 hours after an insult (3) The definition of AKI has evolved over the years depending on the classification used, initially (in 2002) the RIFLE (Risk, Injury, Failure, Loss and end stage) was used, the AKIN (Acute kidney injury network) Classification was developed in 2007. In 2012 both were merged resulting in the kidney disease improving Global Outcome (KDIGO) which is currently in use.(6)

The definition which is currently supported, is supported by the following criteria (KDIGO guidelines):(7)

- Increase in Serum Creatinine by >/= to 0.3 mg/dl (26.5 l mmol /l) within 48 hours; or
- Increase in Serum Creatinine to >/= 1.5 times baseline, which is known; or
- Presumed to have occurred within the prior 7 days; or
- Urine volume 0.5 ml/kg/h for 6 hours.

The KDIGO guidelines were initially adapted for the adult population then pediatric but now modified to the neonatal groups. The peculiar renal pathophysiology of critically ill newborns

makes it difficult to interpret urine output and serum creatinine levels in patients diagnosed with AKI(5)

TABLE 1.1: PROPOSED NEONATAL AKI CLASSIFICATION(2)

Proposed neonatal AKI classification

Stage	SCr	Urine Output
0	No change in SCr or increase <0.3 mg/dL	≥0.5 mL/kg/h
1	SCr increase ≥0.3 mg/dL within 48 h or SCr increase ≥1.5–1.9 × reference SCr[a] within 7 d	<0.5 mL/kg/h for 6–12 h
2	SCr increase ≥2 to 2.9 × reference SCr[a]	<0.5 mL/kg/h for ≥12 h
3	SCr increase ≥3 × reference SCr[a] or SCr ≥2.5 mg/dL or Receipt of dialysis	<0.3 mL/kg/h for ≥24 h or anuria for ≥12 h

[a] Baseline SCr is defined as the lowest previous SCr value.
Modified from Jetton JG, Askenazi DJ. Update on acute kidney injury in the neonate. Curr Opin Pediatr 2012;24(2):191–6.

1.2.1 Risk factors for developing AKI

There are many risk factors that can cause damage to the kidneys. The following have emerged in previous studies:

1) Hypoxia

   Hypoxia secondary to respiratory distress accompanies hypotension and hypovolemia, which negatively influences glomerular hemodynamics leading to AKI.

2) Sepsis

   Selewski *et al.* found that sepsis is a significant cause of morbidity and mortality in neonates with AKI and has been identified in neonates making 78% statistical cases. These neonates are thought to be predisposed to AKI secondary to hypotension associated with systemic inflammation.(3)

   According to a Thailand's study (Vanvanichsanong *et al.*) sepsis-induced AKI had nearly 14 times the risk of death compared to patients with hypovolemia-induced AKI. Sepsis was found to be the most common cause of AKI in their unit. The authors also noted that sepsis with AKI had a higher mortality rate of about 40-56% for newborns with AKI related sepsis.(8)

3) Respiratory distress

Hypoxia and acidosis secondary to respiratory failure contribute to worsening renal dysfunction. Patients who are mechanically ventilated are at a higher risk of AKI. A study done by Tamovska *et al.* confirmed 24% cases of AKI (this is a small study conducted in 24 ventilated neonates.) They also noted higher mortality rate associated with both ventilation and AKI.(9)

4) Drugs: Maternal and neonatal

❖ Maternal

- Indomethacin

In pregnancy the use of indomethacin (which is a non-selective cyclooxygenase inhibitor) as a tocolytic or pain killer adversely affects the unborn baby by causing a reduction of its renal blood flow and glomerular filtration rate (GFR). It was also noted that non-steroidal anti-inflammatory drugs (NSAIDs) predispose neonates to a reduction of their renal output and also AKI.(3)

- Anti-hypertensives

The use of antihypertensive angiotensin converting enzyme (ACE) inhibitor (captopril and enalapril) blocks angiotensin 2, which is kidney protective by maintaining GFR and RFG. There's also a risk of renal agenesis to AKI.(3)

4) Neonatal

Drugs such as Amphotericin B, Aminoglycosides, and ACE inhibitors are nephrotoxic as they cause vasoconstriction of the renal vessels which leads to decreased blood flow through the kidneys.

Based on the study by Akima *et al.*, 2004 demonstrated that 24% of 54 newborns with gestational age <30 weeks and receiving indomethacin for PDA closure developed AKI.(10) This is a prevalence which is quite similar to a study done in Thailand; where 10 out of 41 neonates were studied with gestational age <32 weeks.(8)

5) Birth weight: VLBW and ELBW neonates

Studies done in this group looked at age groups 500g to 1500g:

According to Koralkar *et al., 2011,* a large study that looked at 229 very low birth weight (VLBW) babies as defined by weight of less than 1500g, had incidence of 18% according to KDIGO classification but the mortality was noted to be higher if patient had AKI. (11) Viswanathan *et al.* also reported 12.5% in ELBW (Birth weight of less than 1000g), but the mortality rate was reported to be higher in those neonates. (12)

Koralkar *et al*. Completed another study in VLBW which demonstrated a 18% rate and had a 2.4 increased rate of mortality as compared to other neonatal group with no AKI. (11)

6) Perinatal asphyxia

These groups of patients are recognized as high risk of AKI. The subsequent studies reported the following:

- Kaur *et al.* reported 41.7% incidence of AKI (13) and Selewski *et al.* reported that 38% of 96 cases had AKI in neonates who had undergone therapeutic hypothermia. (14)

- Vanvanichsanong *et al*., 2011 completed a study which took 24 years that reports asphyxia as the most common condition that contributed to AKI (40.0%), followed by sepsis/metabolic disease (22.2%) and feeding problems (17.8%).(15)

7) Extracorporeal membrane oxygenation (ECMO)

The use of ECMO increases the risk of AKI in neonates merely because of the inflammatory response to the exposure to extracorporeal circuit. Zwiers *et al.* performed a study looking at AKI in 242 neonates on ECMO over a 14-year period:
64 % had AKI and 65% were mortality cases when AKI progressed to end stage kidney disease. (16)

8) Neonatal cardiac surgery

Multiple studies have been done to prove the association between AKI and cardiac surgery in children. Alabbas *et al.*, performed a retrospective study where they looked at 122 neonates less than 28 days old and 62% had AKI. The neonates with the end stage of AKI was associated with mortality and increased length of stay in ICU. (17)

1.2.2 Prevention of AKI

There are a number of strategic methods to minimize or reduce the incidence of AKI, especially in the high-risk group:

- Theophylline has proven to have an important therapeutic effect if it is used as prophylaxis in neonates who have suffered from moderate to severe birth asphyxia. However, caution needs to be exercised as theophylline has potential harmful neurologic effects. It is also noted to antagonize the AD receptors (Adenosine) by contrasting renal vasoconstriction both preventatively and during acute kidney injury therefore allowing fast functional recovery. Much research is still required to support this hypothesis;(4)
- Limitation of nephrotoxic drugs and regular monitoring of serum levels of these medications if they are used;
- Diuretics are frequently used to maintain urine output but studies in critically ill patients has demonstrated worse outcomes in neonates with AKI;
- Identification of risk factors, early diagnosis and prevention of AKI improves outcome
- Studies have been done to support antenatal steroids which assist in the maturation of the neonatal kidney;
- Serum creatinine is the most common method to monitor renal function and to diagnose AKI but has shortcomings. It is also noted in the literature that serum creatinine may not change until 25-35% of kidney function has been lost. Serum creatinine also varies by muscle mass, hydration status, age. New Biomarkers have been investigated that give an indication of kidney injury earlier than use of the serum creatinine as a marker of kidney injury. There are a number of biomarkers but the ones that are promising are: Serum and urinary neutrophil Gelatase ass lipocalin(NGAL), Urinary interleukin 18 (IL 18) , Kidney injury molecule (KIM 1) and serum cystatin C(18)

1.3 STUDY AIMS/OBJECTIVES

The aim of this project is:

- To study the incidence of AKI in neonates admitted at the neonatal intensive care unit of Universitas Academic Hospital, from January 2016 to June 2016;
- To determine the risk factors for AKI in neonates admitted in neonatal intensive care from January 2016 to June 2016
- To determine the morbidity and mortality of newborns associated with AKI.
- To make recommendations for the decreasing the incidence of acute kidney injury.

1.4 STUDY METHODS

1.4.1 Study setting

The retrospective study will be undertaken at the neonatal unit, which includes the neonatal intensive care unit (NICU) and neonatal high care unit (NHCU), in Universitas Hospital, Bloemfontein, Free State.

The NICU is a 12-bed unit with a staff to patient ratio of 2-3:1; respectively at most times. The NHCU is a 16-bed unit with 4:1 Staff to patient ratio. These observations are important in the study because better care is attained with medical staff ratio, ideally 1:1.

The amount of fluids given to patients, urinary output and nephrotoxic drugs if not monitored closely may worsen the problem significantly.

1.4.2 Study design

This is a retrospective, descriptive study. Data will be collected from patients' files at Universitas Academic Hospital neonatal and high care filing bank. An excel spreadsheet will be used to enter all qualifying neonates.

1.4.3 Study population

The population selected for this study will include very low birth weight, i.e. weight equal to or less than 1500 g, (VLBW) infants in their first month of life, admitted at Universitas hospital neonatal unit, from January to June. 2016.

The neonatal unit on average admits 12 VLBW neonates per month. This number will give us an adequate sample over the specified time frame. This sample size will be acceptable in order to meet the objectives of the study. This was discussed with a biostatistician.

In Universitas NICU, we routinely take blood samples on the second day of life in VLBW neonates including urea and electrolytes. Every patient admitted will then be reviewed based on their

biochemical results and evaluated according to the inclusion and exclusion criteria for inclusion in the study.

Inc l us i o n cr i t er i a

- Neonates with birth weight of 1500 g or less in their first 30 days of life;
- VLBW babies who have had base line bloods, renal function (urea and electrolytes) in their first 24-48 hours and a repeat of at least two renal function bloods done at least 24 hours apart; and
- VLBW who have had urine output monitoring whilst critically ill.

E x cl us i o n cr i t er i a

- Neonates that are more than 1500 g in weight;
- Patients that are older than 30 days;
- Any patients that do not meet the KDIGO criteria for AKI;
- Patients who demise within 48-72 hours of life
- Any patient with chromosomal abnormalities

1.4.4 Data collection

Data will be collected from the following sources:

- Patient files at Universitas Academic Hospital;
- Discharge summaries from the electronic Meditech system at Universitas Hospital; and ● Patient information from National Health Laboratory services (NHLS).

1.4.5 Statistical analysis plan

Descriptive statistics namely means and standard deviations or medians and percentiles will be calculated for continuous data. Frequencies and percentages will be calculated for categorical data. The analysis will be done by the department of Biostatistics.

1.4.6 Pilot study

As soon as approval is granted by the Ethics committee and the Department of Health, a pilot study will commence. To test for the feasibility of the study six patients who meet the criteria will be entered in an excel spread sheet.
The six patients included in the pilot study will also be part of the study. The purpose of the pilot study will be to:

- Identify possible errors with the data collection process
- To determine the amount of time taken to add a patient to the study
- Identify any necessary adjustments needed to be made for data collection process.

1.4.7 Implementation of findings

Results obtained from this study will provide valuable information regarding the risk factors and management of AKI at Universitas Academic Hospital, the Department of Pediatrics as well as the Department of Health, Free State.
Recommendations will be made to assist with the burden of this devastating disease. Since data from previous studies are limited, this study will also assist in the development of the body of knowledge in this area.

1.4.8 Measurement errors

It is expected that some patients will not have urine output quantified in their files even though these patients meet the criteria AKI criteria.

1.5 ETHICAL CONSIDERATIONS

The study protocol will be submitted to the Health Sciences Research Ethics Committee at the University of the Free State and approval will also be obtained from the Free State Department of Health before the study will commence.

Anonymous archival data, will be used and does not require consent. Approval from the Department of Health provides permission to access the data. It is routine that all patients

admitted in the neonatal unit have bloods taken in their second day of life to look for possible risk factors, no additional tests will be done.

Mentioning of patients' names will not be necessary for our study, only the following data: Gestational age, weight, race, HIV status, maternal history, risk factors involved, ventilated or not.

1.6 BUDGET

The budget for the study includes transport costs, and other miscellaneous costs which will be carried by the Department of Pediatrics and Child Health at the University of the Free State.

TABLE 1.2: PRELIMINARY BUDGET

Transport	R600
Miscellaneous	R400

1.7 TIME SCHEDULE

FIGURE 1.1: PRELIMINARY TIME SCHEDULE

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