The Incidence and Outcomes of Acute Kidney Injury in Critically-Ill Neonates at Chris Hani Baragwanath Academic Hospital: A Prospective Descriptive Study

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Declaration: Student's contribution to article and agreement of co-authors

I, Dr Sanelisiwe Busisiwe Zethu Balfour, student number 1928755, declare that this Research Report is my own work and that I contributed adequately towards research findings published in the article stated below which are included in my Research Report.

Signature of Student ..... Date 23/06/2021

Name of Primary Supervisor: Adj Professor Karen Petersen

Signature of Primary Supervisor ..... Date 21 June 2021

Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article by the student as part of her Research Report. In cases where the student is not the 1st author of a published article, the primary supervisor must explain (under comments) why the student is entitled to use the paper for her degree purposes.

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Comments by primary supervisor:

Dr Balfour worked independently on data collection and most of the analysis. She drafted the manuscript and worked on edits as recommended by supervisors. She fulfills criteria as first author.

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I wish to dedicate this to my partner, Siqhamo Yamkela Ntola, for his unwaivering support and encouragement.

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African Journal of Nephrology guidelines

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An observational study of acute kidney injury in critically-ill neonates at Chris Hani Baragwanath Academic Hospital, South Africa.

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Abstract

Background Acute kidney injury (AKI) is common in critically ill, hospitalized neonates. Scarce epidemiological data exist on AKI in children in South Africa. This study aimed to determine the incidence and outcomes of AKI in critically ill neonates.
Methods This single-centre, prospective, observational study was conducted in the neonatal unit of the tertiary hospital Chris Hani Baragwanath Academic Hospital in South Africa. Neonates with AKI were recruited over a three-month period in 2019. AKI was defined using the AKIN criteria. Risk factors and demographic data were collected for all study participants. Study patients were followed up over the period to observe an outcome of either recovery or death.
Results Fifty-one patients were enrolled. The incidence of AKI was 7.8% (95% CI, 5.9 to 10.2%). The overall mortality of enrolled patients was 29.4% (95% CI, 26.3 to 56.1%), while the mortality rate of enrolled patients with worsening AKI before death was 19.6%. Mortality was significantly associated with extremely low birth weight (OR 11.4, $p<0.01$), umbilical catheterisation (OR 6.3, $p=0.01$), sepsis (OR 5.4, $p=0.01$), phototherapy (OR 4.4, $p=0.03$) and prematurity ($p=0.04$). The most frequent risk factor associated with AKI was intravenous nephrotoxic medication.
Conclusion The incidence of AKI in our study was higher than expected. Further epidemiological and interventional studies are warranted. (231 words)

Keywords Acute kidney injury · Neonate · Creatinine · Incidence · Outcome · Risk factors

Introduction

Currently three classifications exist with regards to diagnosing AKI in neonates, outlined in table 1, namely the neonatal Risk, Injury, Failure, Loss, End Stage (nRIFLE) criteria, the neonatal Kidney Disease: Improving Global Outcomes (nKDIGO) criteria, and lastly the Acute Kidney Injury Network (AKIN) criteria. The classifications characterize AKI into stages based on an increase in serum creatinine (SCr) and a decrease in urine output (UOP) [1]. Prior to 2007 most neonatal studies defined AKI as a rise in SCr of ≥132 umol/l, but since then it was noted that even a small increase in SCr is associated with a poor outcome [2]. Using SCr to diagnose AKI in neonates has its limitations. After birth neonatal SCr reflects maternal levels and over weeks declines at varying rates depending on gestational age, therefore changes in SCr may be difficult to interpret when evaluating AKI [3]. The postnatal decline in serum creatinine, due to changes in glomerular haemodynamics, is less marked in preterm neonates. [4] Non-invasive biomarkers of AKI such as interleukin 8 and cystatin C can predict AKI before SCr rises, but these tests are not widely available and have not been validated in paediatrics in our setting [3,5].

The risk of AKI is increased in neonates [6], with the preterm infant particularly at risk due to incomplete nephrogenesis and immature tubular development [5]. AKI is common in critically ill, hospitalized neonates worldwide, with an incidence that ranges from 2.5% to 74.1% in the Assessment of Worldwide Acute Kidney Epidemiology in Neonates (AWAKEN) database [7]. It is associated with increased mortality and morbidity, increased risk for progression to chronic kidney disease and longer hospital stay [7]. The most common risk factor for AKI is sepsis. Other risk factors include hypovolemia secondary to dehydration, hypoxia secondary to respiratory distress syndrome, patent ductus arteriosus, asphyxia, renal venous thrombosis, nephrotoxic medications, intraventricular haemorrhage and necrotizing enterocolitis [6,8].

Multiple studies have been reported worldwide, especially in the higher-income countries, reporting the incidence of AKI together with risk factors and outcomes [9]. However, there is scarce epidemiological data on AKI in children in middle- and low-income countries, particularly in Africa. A review by Lemeire et al on AKI in children

worldwide found only 21 African studies on paediatric AKI between 2000 and 2014 [9]. A 2016 systematic review of AKI in sub-Saharan Africa identified 22 studies in children [10].

This study aimed to identify the incidence and outcomes of AKI and observe the risk factors in critically ill neonates over a three-month period at Chris Hani Baragwanath Academic Hospital (CHBAH).

Table 1: AKI Classifications

	Stage	SCr/GFR Criteria	UOP Criteria
nRIFLE	Risk	Increased SCr x 1.5 or GFR decreases >25%	UO < 1.5ml/kg/hr x 24hrs
	Injury	Increased SCr x 2 or GFR decreases >50%	UO < 1.0ml/kg/hr x 24hrs
	Failure	Increased SCr x 3 or GFR decreases > 75%	UO < 0.7ml/kg/hr x 24hrs or anuria x 12hrs
	Loss	Persistent failure > 4 weeks	
	End Stage	End stage renal disease (persistent failure > 3 months)	
AKIN	1	SCr increase >26.5umol/l or >1.5-2 times baseline	<0.5ml/kg/hr for 6 hrs
	2	SCr increase >2-3 times baseline	<0.5ml/kg/hr for 12hrs
	3	SCr increase >3 times baseline or SCr >354umol/l with acute increase >44.2umol/l	<0.3ml/kg/hr for 24 hrs or anuria for 12 hrs
nKDIGO	0	No change in SCr or increase <26.5umol/l	>0.5ml/kg/hr
	1	SCr increase > 26.5umol/l within 48 hrs or SCr increase >1.5-1.9 x reference SCr within 7 days	<0.5ml/kg/hr for 6-12 hrs
	2	SCr increase >2-2.9 x reference SCr	<0.5ml/kg/hr for >12hrs
	3	SCr increase >3 x reference SCr or SCr > 221umol/l or receipt of dialysis	<0.3ml/kg/hr for >24hrs or anuria >12hrs

Scr: Serum creatinine; GFR: glomerular filtration rate; UO: urine output; AKIN: acute kidney injury network; nKDIGO: neonatal kidney disease, improving global outcome

Methods

Study Design

This single-centre, prospective, observational study was conducted in the neonatal intensive care unit (NICU) and transitional intensive care unit (TICU) of the tertiary Chris Hani Baragwanath Academic Hospital in Johannesburg, South Africa.

This study was performed in partial fullfillement of the Masters of Medicine (MMed) at the University of the Witwatersrand. Ethics clearance was obtained from the University Human Research Ethics Committee, clearance certificate number M180724.

Population and setting

Patients admitted to the units were screened daily for AKI over the three-month period, between 1 June 2019 to 31 July 2019 and from 1 September 2019 to 30 September 2019, and recruited once consent was obtained.

Exclusion criteria were any patients diagnosed with AKI before the time of data collection, patients older than 28 days old, and patients whose parents or guardians did not provide consent. Demographic data were collected for all the study participants. Written informed consent was obtained from the parents or guardians.

The NICU at CHBAH is an 18-bed unit with approximately 50 admissions per month, while the TICU, which is a high-care unit with a 48-bed capacity including a 6-bed surgical high-care, receives about 200 admissions per month. Patients 1000g and above are offered invasive ventilation while those weighing less than 1000g are offered non-invasive ventilation.

Study patients were followed up over the three-month period to observe an outcome of either recovery or death.

Definitions

Neonatal AKI was diagnosed by the rise in serum creatinine and classified using AKIN criteria. Patients were also enrolled if the baseline serum creatinine value was ≥132umol/l and classified into one of the AKIN stages based on the local neonatal SCr reference intervals obtained from the National Health Laboratory Services (NHLS). The latter definition was included to include patients who did not have a baseline serum creatinine. The AKIN classification was used as it gives more specific rises in SCr values as nRIFLE. Additionally, KDIGO classifications use SCr rise in baseline level over 7 days, whereas AKIN includes similar rises in 48 hours. Although KDIGO would have allowed for more AKI patients to be detected, AKIN was appropriate for our limited time constraints with regards to the study period.

Critically-ill was defined as a patient requiring admission to ICU due to severe respiratory, cardiovascular, or neurological derangement, reflected in abnormal physiological observations [11].

Spurious SCr results due to delays in specimen processing were not included in the analysis.

Risk factors were defined using the CHBAH Neonatal Protocols by Nakwa et al [12]. Sepsis was defined as confirmation of a microorganism on a positive blood culture. Hypotension was defined as a mean arterial pressure (MAP) of $<10^{th}$ percentile for age, gestation or birth weight subsequently requiring inotropic support. Hypoxaemia was characterized by those neonates requiring supplemental oxygen. Asphyxia was defined as a 5-minute Apgar of <5 or a blood gas within 1 hour of life with a pH <7.0. Nephrotoxic medications noted were Gentamicin, Vancomycin, Amphotericin B or Colistin. Umbilical lines included a venous line and/or an arterial line. Surgical patients included all subspecialities except cardiothoracic surgery.

Extremely low birth weight (ELBW) was defined as a birth weight of less than 1000g, very low birth weight (VLBW) between 1000g to 1499g, low birth weight (LBW) between 1500g to 2499g, and normal birth weight between 2500g and 3999g. Prematurity was defined as a gestational age of less than 37 completed weeks at birth.

Although there are limitations when defining recovery of AKI we used Forni et al and defined full recovery as the absence of AKI criteria and partial recovery as a fall in AKI stage [13]. Outcome was either recovery or death.

Serum creatinine was analysed by the National Health Laboratory Services by utilizing the enzymatic reaction method from the Roche/Hitachi Cobas C systems. Serum creatinine was measured on day two of life to avoid representation of maternal creatinine.

Statistical Analysis

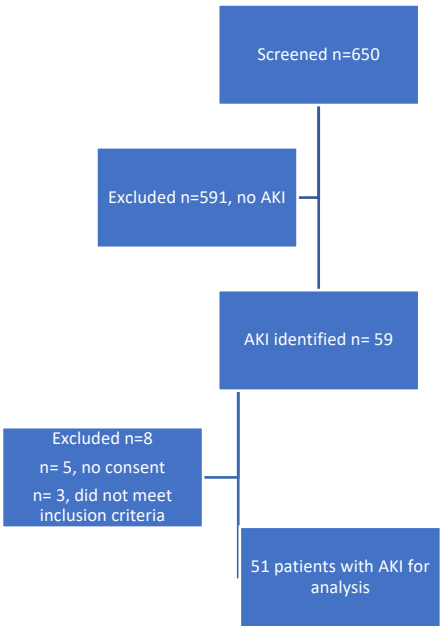
Sample size was estimated at 45 if a 5% margin of error was accepted and a 95% confidence level to detect an incidence of 3%. Incidence and mortality rate was accompanied by 95% confidence interval (95% CI). A value of $p<0.05$ was considered as statistically significant. Categorical variables were expressed as percentages and frequencies. Continuous variables, depending on the normality of distribution, were expressed as mean $\pm$ standard deviation or median with interquartile ranges. Differences between categorical variables were calculated using the Chi-squared test or Fischer exact test. A univariate logistic regression was used for the association between risk factors and mortality, and results of the analysis were expressed as odds ratios with a 95% CI. STATA Version V16 was used for all data analysis.

Results

Incidence of AKI

Over the three-month duration of the study 650 patients were screened as consecutive admissions to TICU and NICU, and of these admissions 59 patients were diagnosed with AKI. Eight were excluded from the study: three did not meet the inclusion criteria, and consent was not obtained from five patients, therefore 51 patients were used in the final analysis, figure 1. The incidence of AKI in critically ill neonates at CHBAH over a three-month period was 7.8% (95% CI, 5.9 to 10.2%).

Figure 1: Study patient enrollment



Patient characteristics

Table 2 summarizes patient characteristics. Of the 51 neonates enrolled 27 (52.9%) were male. The mean (SD) gestational age was 31.8 (5.4) weeks, the median (IQR)

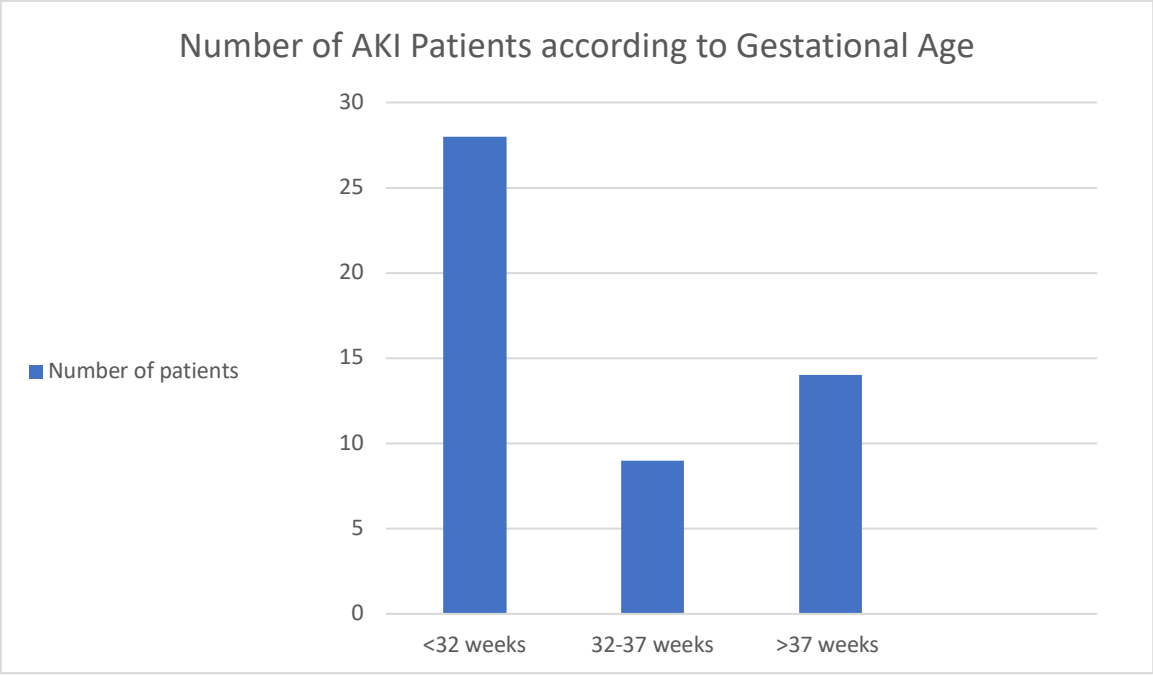
birth weight was 1220 (905 to 2490) grams. The mean (SD) serum creatinine at diagnosis was 142.9 (39.7) umol/l. The median (IQR) final SCr at outcome was 71 (53 to 113) umol/l. According to the AKIN criteria 36 (70.6%) patients were classified as stage 1 AKI, 12 (23.5%) patients as stage 2, and three (5.9%) patients as stage 3 AKI. Eighteen (35.3%) of the patients were ELBW neonates and 37 (72.5%) were premature. Figure 2 shows the distribution of gestational age, with 28 (55.0%) patients less than 32 weeks' gestation.

Table 2: Acute Kidney Injury Patient characteristics

Characteristic	**AKI N = 51**
Male sex, n (%)	27 (52.9)
Birth weight (grams), mean (SD)	1220.0 (905 to 2490)
<1000g, n (%)	18 (35.3)
1000-1499g, n (%)	10 (19.6)
1500-2499g, n (%)	11 (21.5)
2500-4000g, n (%)	12 (23.5)
Gestational age (weeks), median (IQR)	31.8 (±5.4)
<26 weeks, n (%)	4 (7.8)
26-32 weeks, n (%)	24 (47.1)
>32-37 weeks, n (%)	9 (17.6)
>37 weeks, n (%)	14(27.5)
Lowest pre-AKI creatinine (umol/l), mean (SD)	107.4 (±43.2)
Diagnosis creatinine (umol/L), mean (SD)	142.9 (±39.7)
Final creatinine (umol/l), median (IQR)	71 (53 to 113)
AKI Stage	
Stage 1, n (%)	36 (70.6)
Stage 2, n (%)	12 (23.5)
Stage 3, n (%)	3 (5.9)

SD: standard deviation; IQR: interquartile range

Figure 2: Number of AKI patients according to gestational age



Outcomes

The end points of follow up were defined as recovery or death, 36 (70.6%) patients recovered and 15 (29.4%) patients died. The in-hospital mortality rate of enrolled patients was 29.4% (95% CI, 26.3 to 56.1%) while the mortality rate of enrolled patients with worsening AKI before death was 19.6% (n=10). The neonatal mortality rate in TICU and NICU over the three-month period was 16.2 per 1000 live births. The median (IQR) age at diagnosis of AKI was three (2 to 5) days. Forty-five (88.2%) patients developed AKI in the first week of life, three (5.9%) in the second week, two (3.9%) in the third week and one (2.0%) in the fourth week. The median (IQR) end point time was six (5 to 11) days. The median (IQR) time to recovery was seven (5.0 to 11.5) days and the mean (SD) time to death was 6.1 (2.5) days.

Of those in stage 1 AKI eight (22.2%) died, in stage 2 AKI six (50.0%) died, and in stage 3 AKI one (33.3%) died. The severity of AKI is an independent risk factor for poor outcome [6]. This could not be analysed in this study due to the small sample size, with only three patients in stage 3.

In the group who died (n= 15), five (33.3%) showed recovery of SCr before death, while 10 (66.7%) showed a worsening SCr before death. The ten patients who died with worsening AKI were not dialysed due to extreme prematurity n=7, profound neurological impairement n= 2, and one who died on the day of diagnosis.

Risk Factors

All enrolled patients had more than one risk factor identified. The most frequent risk factor associated with AKI was intravenous nephrotoxic medication, with Gentamicin being the most widely used. The second most common risk factor was hypoxia as 49 (96.0%) patients required supplementary oxygen at birth, figure 3. The group that died had a mean (SD) of 5.1 (0.7) risk factors per patient compared to 3.4 (1.1) in those who recovered ($p<0.001$). Table 3 summarizes the individual risk factors per outcome group. A univariate logistic regression was used for the association between risk factors and mortality. The risk factors significantly associated with mortality were ELBW (OR 11.4, 95% CI 2.8 to 46.7, $p<0.001$), umbilical lines (OR 6.3, 95% CI 1.6 to 24.0, $p=0.01$), sepsis (OR 5.4, 95% CI 1.4 to 21.7, $p=0.01$), and phototherapy (OR 4.4, 95% CI 1.1 to 16.7, $p=0.03$). Twelve (92.3%) of the 13 patients who received phototherapy were premature. More premature patients with AKI died compared to term neonates (37.8% vs 7.1%, $p=0.04$).

Figure 3: Patient risk factors

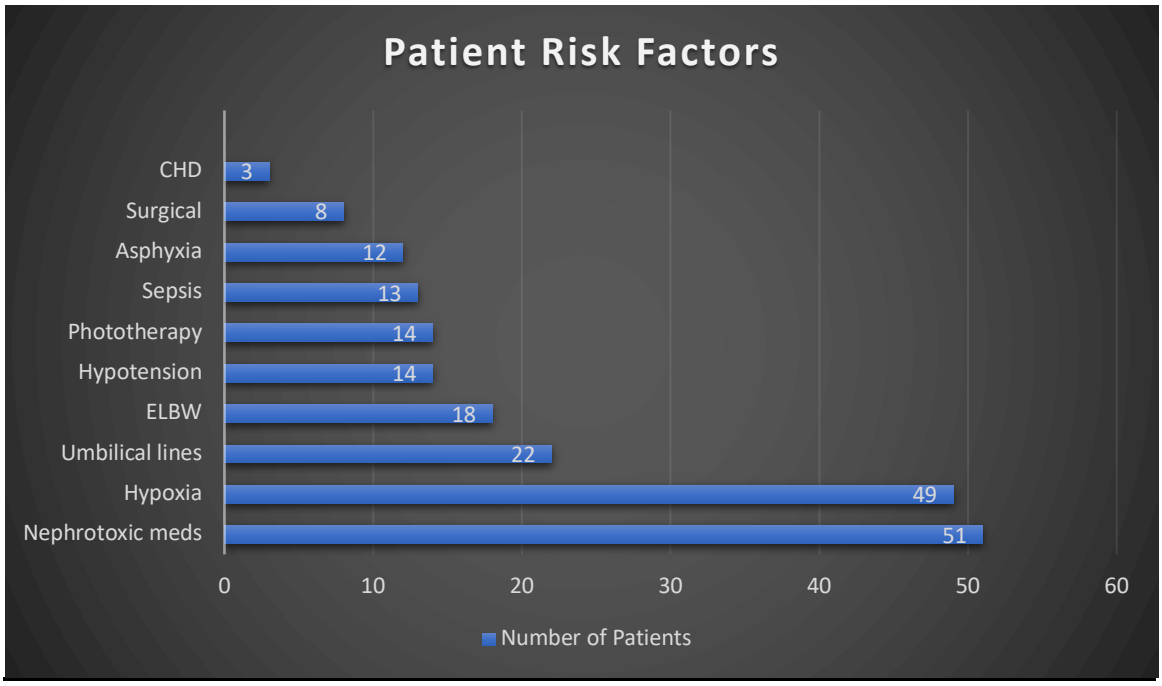


Table 3: Risk factors and Acute Kidney Injury stage per outcome group

Risk Factor	Recovered=36 n (%)	Died=15 n (%)	P value	Odds Ratio, 95% CI
Sepsis	5 (13.9)	7 (46.7)	0.01	5.4 (1.4 to 21.7)
Hypotension	9 (25.0)	5 (33.3)	0.54	1.5 (0.4 to 5.6)
Hypoxia	35 (97.2)	15 (100)	1.00	N/A
Asphyxia	4 (11.1)	4 (26.7)	0.16	2.9 (0.6 to 13.7)
Nephrotoxic Drugs	36 (100)	15 (100)	0.31	N/A
Umbilical lines	11 (30.5)	11 (73.3)	0.01	6.3 (1.6 to 24.0)
ELBW	7 (19.4)	11 (73.3)	0.001	11.4 (2.8 to 46.7)
Phototherapy	6 (16.7)	7 (46.7)	0.03	4.4 (1.1 to 16.7)
CHD	3 (8.3)	0 (0)	0.55	N/A
Surgical	6 (16.7)	0 (0)	0.16	N/A
Prematurity	23 (63.9)	14 (93.3)	0.04	7.9 (0.9 to 67.2)

ELBW: extremely low birth weight. PTT: phototherapy. CHD: congenital heart disease. N/A: unable to assess Odds Ratio as 100% of patients had the risk factor or there was very little difference between groups.

Discussion

The incidence of AKI in critically ill neonates varies and has been reported to differ at multiple centres [7], with Momtaz et al reporting an incidence as low as 1.5% in their study [8] and Shalaby et al reporting an incidence of as high as 54% in a tertiary NICU in Saudi Arabia, a high-income country, using the nKDIGO classification [6]. The difference in incidence varies according to the population studied and definitions used [6,14], therefore a general consensus needs to exist regarding the definition of neonatal AKI. Shalaby et al and Bolat et al documented mortalities of 28% and 23.8% in Turkey and Saudi Arabia amongst neonates with AKI [6,14], similar to our findings. The AWAKEN trial documented a mortality rate as low as 9.7% but this could be explained by the inclusion of multiple centres including high-income countries [7].

In this study group, neonates were particularly at risk of developing and dying from AKI in the first week of life. Meticulous attention should be paid to limiting the risk factors during this time.

Since all enrolled neonates were exposed to multiple known risk factors, logistic regression was used to determine variables associated with mortality and identified patients with ELBW, umbilical line catheterisation, sepsis, and phototherapy to be at an increased risk of death. Other studies documented similar associations with sepsis and ELBW [6,7,15]. However, phototherapy is not a well-documented risk factor. This may be confounded by prematurity since almost all patients who received phototherapy were premature. Premature neonates with AKI were more likely to die compared to term neonates, even after recovery of kidney function. It is well known that prematurity is an independent risk factor for mortality [6]. Although nephrotoxic medication was the most frequent exposure variable, it was not associated with mortality. This is likely due to the unit policy of measuring drug levels and limiting empiric antibitoic use to 48 hours where possible..

This U-shaped distribution to the incidence with a higher incidence amongst the extremes of gestation is similar to the AWAKEN study [7]. An explanation to term neonates having a higher incidence, but better survival, than late prems could be that term infants requiring ICU were critically-ill, unstable and in need of higher levels of care whereas the premature infants at times required ICU as a result of ventilatory support due to respiratory distress syndrome.

Of note, congenital anomalies of the kidney and urinaty tract (CAKUT) were not diagnosed in any of the enrolled patients. This may be underestimated due to the low rate of antenatal ultrasounds [16] and possible delays in postnatal ultrasounds. Okoronkwo et al [17] reported CAKUT in 20% of patients referred to the Paediatric renal unit over a 10-year period at Charlotte Maxeke Johannesburg Academic Hospital. The short study period may have contributed to the absence of underlying CAKUT in this cohort. In addition, not all patients with CAKUT develop AKI [18,19].

This study documents the incidence of AKI in critically-ill neonates in South Africa, and reports on the risk factors and outcomes in this study population. It identifies risk factors as areas of intervention for further studies to improve the outcome in this group. However, limitations are noted. The limitations of serum creatinine are universal. Limitations of this study includes the small sample size. We used an incidence rate of 3% based on studies from mainly developed countries [1,2,3,7,8]. The paucity of studies from developing countries resulted in an incidence higher than expected and an underestimation of sample size. Using the incidence rate from this study, the calculated sample size would be 110 patients. The small sample size limited the statistical analysis of risk factors. Additionally, urine ouptut was not used to identify patients with AKI. Urine output measurement is cumbersome in the newborn as it requires urinary cathetersation and is invasive and time consuming [4]. Including urine output to identify AKI may have resulted in a higher incidence rate. Additionally, this study included patients admitted to the high care area TICU. This may have resulted in an underestimation of the incidence rate. However, it should be noted that all the ELBW neonates were enrolled from this area. Another limitation is the lack of long-term follow-up to assess outcome, particularly progression to chronic

kidney disease. Despite these limitations, this study can form the basis of future studies by applying the incidence rates, risk factors and outcomes in critically-ill neonates with AKI.

Conclusion

The incidence of AKI in critically ill newborns at CHBAH during the three-month period was 7.8% with a recovery rate of 70.6%, and an overall in-hospital mortality of 29.4%. The incidence of AKI in the neonate may be decreased by addressing the risk factors associated with AKI. More epidemiological and interventional studies are needed to identify and improve the long-term outcome of AKI in the newborn in our setting.

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None.

Conflict of interest

The authors declare that they have no conflict of interest.

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ABBREVIATIONS

AKI	Acute Kidney Injury
CHBAH	Chris Hani Baragwanath Academic Hospital
TICU	Transitional Intensive Care Unit
NICU	Neonatal Intensive Care Unit
GFR	Glomerular Filtration Rate
SCr	Serum Creatinine
UOP	Urine Output
AKIN	Acute Kidney Injury Network
nKDIGO	Neonatal Kidney Disease: Improving Global Outcomes
p/nRIFLE	Paediatric/Neonatal Risk, Injury, Failure, Loss, End Stage Renal Disease
ADQI	Acute Dialysis Quality Initiative
RDS	Respiratory Distress Syndrome
NEC	Necrotizing Enterocolitis
HIE	Hypoxic Ischaemic Encephalopathy
RRT	Renal Replacement Therapy
ELBW	Extremely Low Birth Weight
VLBW	Very Low Birth Weight

Research Protocol

1) Introduction

Definition

Acute kidney injury (AKI) is characterised by the rapid decline in the ability of the kidneys to maintain homeostasis of water and electrolytes, associated with a reduction of the glomerular filtration rate (GFR)[1] resulting in the accumulation of nitrogenous waste products, derangement in fluid balance and the loss of electrolytes and acid-base homeostasis[2]. Previously termed acute renal failure (ARF), in most recent classifications the term “failure” is reserved for those cases requiring renal replacement therapy (RRT) or dialysis[3].

Diagnosis

There are great difficulties present in the diagnosis of AKI, especially in the neonatal period[3]. Currently the diagnosis of AKI is defined by a rise in serum creatinine (SCr) and/or a decrease in urine output (UOP)[4]. There are several classifications of neonatal AKI and there is no generally accepted opinion so far as to which criteria (SCr, UOP or a combination) are the most appropriate to diagnose neonatal AKI[2]. AKI standardised definitions are based largely on paediatric Risk, Injury, Failure, Loss, End Stage Renal Disease (pRIFLE) recently adapted to formulate neonatal RIFLE (nRIFLE), Acute Kidney Injury Network (AKIN), and Kidney Disease: Improving Global Outcomes (KDIGO) classifications respectively[5].

Prior to 2007 most neonatal AKI studies defined AKI as a rise in SCr of >132umol/l but since then it was noted that even a small increase in SCr is associated with a poor outcome[2]. New criteria were then introduced based on SCr and UOP, with particular importance on the way that even an incremental rise in SCr can be of significance and how different severities of AKI can result in different outcomes[3].

Below are the three current classifications used in diagnosing neonatal AKI:

The **RIFLE criteria** was proposed by the Acute Dialysis Quality Initiative (ADQI) in 2004[3]. Three years later it was modified into a paediatric version, pRIFLE, and later a neonatal version, nRIFLE[3], by Ackan-Afrikan et al, based on the decrease in the estimated creatinine clearance and the urine output[5]. Three levels of kidney injury (risk, injury, failure) and two outcomes (loss of kidney function and end stage renal failure) have been graded according to the RIFLE criteria[5]. (Table 1)

The **AKIN Criteria** proposed by the Acute Kidney Injury Network defines AKI based on the increase in SCr and the decrease in UOP. Three stages exist according to increasing severity from stage 1 to stage 3. (Table 1)

In 2013 the **KDIGO** clinical practice guidelines workgroup proposed and published a definition combining AKIN and RIFLE aspects thus providing one tool used both in clinical practice and research[3]. (Table 1)

Table 1

	Stage	**SCr/GFR Criteria**	**UOP Criteria**
nRIFLE	Risk	Increased SCr x 1.5 or GFR decreases >25%	UO < 1.5ml/kg/hr x 24hrs
	Injury	Increased SCr x 2 or GFR decreases >50%	UO < 1.0ml/kg/hr x 24hrs
	Failure	Increased SCr x 3 or GFR decreases > 75%	UO < 0.7ml/kg/hr x 24hrs or anuria x 12hrs
	Loss	Persistent failure > 4 weeks	
	End Stage	End stage renal disease (persistent failure > 3 months)	
AKIN	1	SCr increase >26.5umol/l or >1.5-2 times baseline	<0.5ml/kg/hr for 6 hrs
	2	SCr increase >2-3 times baseline	<0.5ml/kg/hr for 12hrs
	3	SCr increase >3 times baseline or SCr >354umol/l with acute increase >44.2umol/l	<0.3ml/kg/hr for 24 hrs or anuria for 12 hrs
nKDIGO	0	No change in SCr or increase <26.5umol/l	>0.5ml/kg/hr
	1	SCr increase > 26.5umol/l within 48 hrs or SCr increase >1.5-1.9 x reference SCr within 7 days	<0.5ml/kg/hr for 6-12 hrs
	2	SCr increase >2-2.9 x reference SCr	<0.5ml/kg/hr for >12hrs
	3	SCr increase >3 x reference SCr or SCr > 221umol/l or receipt of dialysis	<0.3ml/kg/hr for >24hrs or anuria >12hrs

KDIGO classifications use SCr rise in baseline level over 7 days, whereas AKIN includes similar rises in 48 hours, therefore KDIGO could be more inclusive[7] by detecting more patients with AKI.

Important factors to be considered with any neonatal AKI definition:

1: Markers of GFR including Creatinine

Using SCr to diagnose AKI in neonates poses challenges. After birth neonatal SCr reflects maternal levels over weeks declining at varying rates as the kidney matures, therefore changes in SCr may be difficult to interpret when evaluating AKI[6]. In addition, when using the Jaffe method to measure SCr, high bilirubin levels in the neonatal period may alter its interpretation[3]. Furthermore, SCr is a late marker of renal damage and takes days to rise after an injury has occurred, thus the focus has been to find better AKI biomarkers to diagnose the process earlier[6]. Serum and urinary neutrophil gelatinase-associated lipocalin (NGAL), Osteopontin (OPN), urinary interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1) and serum cystatin-C are early non-invasive biomarkers of AKI[3] and can predict AKI in infants before SCr rises, but tests to detect this are not widely available[6] especially in our setting in South Africa. The use of these biomarkers will improve our ability to diagnose AKI and improve outcomes[3].

2: Urine Output

With regards to using UOP when diagnosing AKI, there are many challenges. Neonates commonly have non-oliguric renal failure, making oliguria an insensitive marker of AKI[6]. The reduction of urine output can be observed in the absence of AKI therefore it cannot be used as the only criterion for assessment[1]. Finally, urinary catheters are rarely used in newborns and UOP is assessed by nappy weighing, which is very inaccurate[2]. The use of either UOP or SCr to diagnose AKI has a low sensitivity value for prediction of a poor outcome. The combination of SCr and UOP were more specific in predicting death compared to using only SCr or UOP criteria[2]. Many studies have failed to come to similar conclusions as different classifications

are used and the above shortcomings exist. An important step moving forward is the development of one standardised definition and diagnostic criteria for AKI[4].

Aetiology

The causes of AKI are divided into pre-renal, intrinsic and post-renal. The frequency with which each type occurs differs by age group[5]. Pre-renal failure is the most common form and is due to a reduction in intravascular volume leading to renal hypoperfusion [3,5]. Intrinsic renal failure accompanies an intrinsic organ injury to the renal parenchyma as a result of prolonged renal hypoperfusion, ischaemia and direct tubular injury [3,5]. Post-renal failure is due to obstructive uropathies[5].

Risk factors/Causes[1-9] of AKI can be divided into three main categories based on their aetiology, namely shock, hypoxia and drugs. These aetiological causes act through many complex pathophysiological pathways that results in AKI[3].

Sepsis was found to be the most common predisposing factor, with a prevalence of up to 77.5% in hospitalised newborns with AKI[1]. Preterm infants are more likely to develop AKI as they usually require ICU admission, are more prone to develop sepsis with or without necrotizing enterocolitis (NEC) and hypotension, in addition to receiving nephrotoxic drugs[1] and have incomplete nephrogenesis[4]. Hypotension and dehydration (due to inadequate fluid administration or increased insensible losses due to phototherapy) were also noted to be risk factors of developing AKI[1,3,4.]

Hypoxia secondary to respiratory distress syndrome (RDS) as well as hypoxia from perinatal asphyxia have been proven to be risk factors for developing AKI[1,3,4.]

Nephrotoxic drugs commonly used in the neonatal ICU have been shown to predispose patients to AKI, namely Gentamicin, Vancomycin and Amphotericin B[4]. The use of NSAIDS during the neonatal period or during pregnancy is known to also be a risk factor for AKI in neonates[3].

The preterm infant is particularly at risk due to incomplete nephrogenesis and immature tubular development[3].

Incidence

Neonatal AKI is very common with an incidence as high as 54% among neonates hospitalised in NICU's worldwide[2]. There have been a number of single-centre reports on the impact of AKI in certain groups of infants, as described below.

Developing/Low-Income Countries

There is scarce epidemiological data on AKI in children and adults in middle- and low-income countries, with a lower number of African studies on paediatric AKI. A review by Lemeire et al on AKI in children worldwide found only 21 African studies on paediatric AKI between 2000 and 2014. Most African studies originate from tertiary or university hospitals with a renal service and therefore do not reflect the reality of the entire country[16]

VLBW Neonates

The incidence of AKI was 11.6% of 293 very low birth weight (VLBW) infants in an NICU in the United Arab Emirates[9] and in 18% of VLBW infants in an NICU in Birmingham[14]. In extremely low birth weight (ELBW) infants in an NICU in Cleveland Ohio, an incidence of as high as 49%[7] was found.

Perinatal Depression

Infants with perinatal asphyxia have been identified as a group at risk for AKI[4]. Kaur et al evaluated neonates 34 weeks gestational age or more in a neonatal unit of a teaching hospital in India with one-minute Apgar scores less than seven. They found that AKI developed in 9.1% of patients with moderate asphyxia and 56% of patients with severe asphyxia[14]. In a Children's Hospital in Michigan, newborns undergoing

therapeutic hypothermia for asphyxia were evaluated and it was found that 38% had AKI[15].

Prognosis

The natural progression of patients with AKI is either resolution, progression to chronic kidney disease (CKD) or death[6,7].

The length of hospital stay is significantly longer in patients who develop AKI[9]. Of those infants who survived and had resolution of AKI, it was found in one study that AKI is associated with growth failure upon discharge from hospital although catch-up growth was achieved by three years of age[7]. The prognosis of AKI in neonates is worse than in adults, therefore it is important to prevent AKI by rapid diagnosis of patients with risk factors and effective treatment[1]. Children who survive AKI are at an increased risk for developing CKD[4]. Even small changes in SCr were associated with increased mortality and morbidity[4].

There is a significant mortality rate with a documented 42% in VLBW infants with AKI in Birmingham[6,13]. The leading cause of death in neonates with AKI includes sepsis, prematurity and asphyxia, which is consistent with the leading causes of death in all newborns[1]. The mortality rate was found to be higher in low birth weight patients[9], patients with a worse general condition, and more severe underlying disease[1].

In conclusion, multiple single-centre studies have been reported worldwide, especially in the developed world, highlighting the incidence of AKI together with risk factors and outcomes. Very few published data exist in the developing countries, including South Africa. More epidemiological studies are needed to identify the burden of AKI in the newborn[16].

2) Aims and Objectives

Aims

The aim of this study is to calculate the incidence of AKI in critically-ill patients in the neonatal intensive care unit (NICU) and the transitional intensive care unit (TICU) at

Chris Hani Baragwanath Academic Hospital (CHBAH), and to document the outcome of each patient.

Objectives

The objectives of this study are to

1: Identify patients with AKI, as defined by a random SCr >132umol/l or the AKIN SCr criteria defined by a SCr rise of at least 26.5umol/l (see Table 1)

2: Calculate the incidence of AKI in the critically-ill patients admitted to TICU and NICU

3: Document outcomes of each patient

3) Methods

Study Design

The study will be a prospective descriptive and analytical study. Over the research period, all ill-patients admitted to TICU and NICU for a prolonged amount of time (e.g. ELBW, perinatal asphyxia, RDS) will be screened on a daily basis and on days when I cannot be present, I will recruit the help of colleagues working in NICU and TICU to inform me of patients that they have screened and identified as having AKI.

Study Population

The study population will include all patients diagnosed with AKI admitted to CHBAH NICU and TICU within the time period. Approximately 250 patients and 50 patients are admitted to TICU and NICU respectively per month. Patients will be screened according to urea, creatinine & electrolytes, done routinely on day two of life for ill patients, patients who are admitted for a prolonged amount of time and patients at risk for sepsis, as well as any SCr repeated thereafter. Exclusion criteria will be patients diagnosed with AKI before the time of data collection, patients admitted to the unit without AKI, patients older than 28 days, and patients whose guardians do not provide consent.

Definition

The diagnosis of AKI will be characterised by a SCr of >132umol/l or using the SCr AKIN criteria as outlined previously. SCr is currently measured at the chemistry laboratory at CHBAH by the Roche COBAS machines using the Jaffe reaction method which is a chemical reaction using an alkaline medium which forms a yellow-orange complex. The rate of dye formation is proportional to the creatinine concentration in the specimen. This method of measuring creatinine has interferences, by bilirubin, ketones and drugs, therefore the laboratory will soon use the enzymatic reaction method, which is currently being used to calculate creatinine in most private laboratories[10,19]. When using the Jaffe method the Schwartz formula should be used to calculate GFR[19].

4) Data Collection

Data will be collected upon entry of the study using an adapted data collection sheet (See appendix A). From these patients, the incidence rate of AKI will be calculated from the total admissions to TICU and NICU for those months. These patients will then be followed up during this time period until an outcome is identified, namely either resolution, chronic kidney disease or death. Telephonic consent will be obtained from parents if they are not available in the unit. Computer screening of last SCr of patients will be done on the laboratory system.

5) Statistics

The incidence of AKI in critically-ill patients will be represented as an incidence rate, calculated using the number of patients newly diagnosed with AKI from the total admissions of patients admitted to TICU and NICU. The continuous variables will be measured as a mean with a 95% confidence +-SD interval and will additionally be presented as box plots. The categorical values will be represented as frequency tables and differences calculated using the Chi-squared test. The outcomes of the patients will be represented using bar graphs. I will use the STROBE Guidelines for the reporting of my study[18].

6) Ethics

Informed consent will be obtained from the guardian of the patient (See appendix B). For this study each patient will remain confidential and a number will be assigned to them on the data collection sheet. All information needed for this study will be collected from the patient's file and blood results sheets which will be kept with each patient at their bedside throughout their admission at the NICU and TICU. Permission to use these files will be requested from the Department of Neonatology at CHBAH, the CHBAH management, and the Gauteng Department of Health (GDH). Approval will be requested from the Medical Human Research and Ethics Committee (HREC) at the University of the Witwatersrand. Plagiarism will be avoided by referencing appropriately and submitting via Turn It In.

7) Funding

All funding will be provided for by the student, namely photocopying funds. No staff will be employed and all data collection and consent will be performed by the student.

8) Limitations

Due to the prospective nature of this study, the allocated two months research leave may limit the sample size. The definition of AKI based on SCr alone may mean that some patients with AKI based on UOP criteria may be missed. Baseline SCr is performed on ill patients, patients at risk for sepsis as well as patients who require a prolonged hospital stay admitted to NICU and TICU but a repeat SCr is not routinely done if the initial results are normal, therefore we may not identify patients with AKI based on the AKIN criteria of a rise in baseline. With the study being prospective in nature it will require me to be present at most times, my absence will be circumvented by me using a screening book upon my return and relying on colleagues to inform me of patients newly diagnosed with AKI.

9) Timeline

Oct 2017	Nov 2017	Dec 2017	May 2018	May 2018	Nov 2018	Dec 2018	Jan 2019	Mar 2019
Literature review								
	Protocol preparation	Protocol preparation						
			Protocol submission to CHBAH, GDH, Dept of Neonates, HREC & post-grad committee assessment					
				Ethics application				
					Data collection	Data collection		
							Data analysis	
								Write up & submission

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Appendix A

The Incidence of Acute Kidney Injury and Outcome in Critically-Ill Neonates at Chris Hani Baragwanath Hospital: A Descriptive Study

Data Collection Sheet

Patient File Number _____

Mom's File Number _____

Bed _____

Patient Characteristics

Date of Birth	
Gestational Age	
Sex	
Birth Weight	

AKIN 1	
AKIN 2	
AKIN 3	

1)Initial SCr		**Date**
2)Lowest SCr		**Date**
3)Diagnosis SCr		**Date**
4) Final Scr		**Date**

Risk Factors

Sepsis (Confirmed positive blood culture)[21]	**Yes**		**No**	
Hypotension (Mean arterial pressure <10th percentile for age, gestation or birth weight)[21]	**Yes**		**No**	
Hypoxia secondary to RDS (Requiring supplemental O2)	**Yes**		**No**	
Asphyxia (Apgar <5 at 5 mins or blood gas ph<7.0)[21]	**Yes**		**No**	
Nephrotoxic medication (Gentamycin, Vancomycin, Amphotericin B)	**Yes**		**No**	
Umbilical lines (UVL or UAL)	**Yes**		**No**	
Other:				

Outcome

	Yes	Date (Day of Life)
Resolution		
CKD		
Death		

Urine Dipstix

pH	
Blood	
Leukocytes	
Protein	
Bilirubin	
Glucose	
Bilirubin	

Appendix B

The Incidence and Outcomes of Acute Kidney Injury in Critically-Ill Neonates at Chris Hani Baragwanath Academic Hospital: A Prospective Descriptive Study

Information Sheet

University of the Witwatersrand

Principal Researcher: Dr SBZ Balfour
Paediatric Registrar
Department of Paediatrics
Email: nellie.balfour@yahoo.com
Cell: 0826418149

Good day

This informed consent form is for the parents/guardians of newborns with Acute Kidney Injury (AKI) admitted to the Neonatal Intensive Care Unit (NICU) and Transitional Care Unit (TICU) at Chris Hani Baragwanath Academic Hospital (CHBAH).

My name is Dr Sanelisiwe Balfour and I am conducting a study on acute kidney injury in newborns admitted to the neonatal ICU and transitional ICU at Chris Hani Baragwanath Academic Hospital, as part of my requirement to gain a Masters in Medicine degree from the University of the Witwatersrand.

Acute kidney injury is common in infants in the ICU and at times may carry a poor outcome in very ill babies. Studies have been done around the world looking at risk factors in order to try and prevent the poor outcome and progression of the disease. Few studies have been conducted in our setting. The study I am conducting aims to identify the occurrence of AKI as it is important that we better try and understand this condition to help further patients in our setting.

I am inviting you to have your child participate in this study. If you have any questions or if there is anything you do not understand, feel free to ask me and I will be more than happy to explain. You are under no obligation to take part in this project and you have the right to withdraw at any time.

Your decision to have your child participate in this study is completely voluntary. Whether or not you choose to consent, the services your child receives at this hospital will remain the same and will continue. Your child, as a patient of the hospital, will already have routine blood sampling by the doctors. What I require is the patient's file and blood results. Your child's personal details will not be used in the results of the study. No procedures will be done on your child by me and I may never see the child. Your child's hospital stay or state of health will not be affected by the study and the study carries no risks as there are no interventions done by me. You will not be provided with any financial incentive for participation in this project, nor will it cost you anything.

The data I use from patient records will be secured in a locked filing cabinet and will only be accessible to me and my supervisors for this study, Drs Karen Petersen and Dr Letlhogonolo Sepeng. I will write up the report based on this data and you are welcome to see a summary of the report if you wish. No child will be identified by name on this report.

If you have any questions please contact me, Dr S Balfour by cellphone on 0826418149, or by email at nellie.balfour@yahoo.com, or my supervisors, on email at Karen.Petersen@wits.ac.za, Letlhogonolo.Sepeng@wits.ac.za or by telephone at 0119338400.

The study has been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg. The main function of this committee is to protect the rights and dignity of all human subjects who agree to participate in a research project and the integrity of the research.

If you have any concern over the way the study is being conducted, please contact the Chairperson of this committee who is Professor Clement Penny, who may be contacted on telephone number 011 717 2301, or by email on

Clement.Penny@wits.ac.za. The telephone numbers for the committee secretariat are 011 717 2700/1234 and the email adddresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za.

If you agree that I may access your child's data, I will ask you to sign a document called the Informed Consent Sheet.

Thank you for reading this Study Information Sheet

Appendix C

University of Witwatersrand

The Incidence of Acute Kidney Injury and Outcome in Critically-Ill Neonates at Chris Hani Baragwanath Hospital: An Observational Descriptive Study

Guardian of Participant

I, _____ have read the information or have been read the information regarding the study on AKI by Dr Balfour. I have had the opportunity to ask questions and my questions have been answered to my satisfaction. I consent voluntarily to my child being a participant in this study.

Print Name of Participant _____

Print Name of Guardian _____

Signature of Guardian _____

Date _____

Researcher

I Dr S Balfour have accurately read out the information sheet to the guardian of the participant as best as I can to convey all the information. I confirm the guardian was given an opportunity to ask questions about the study and I answered them to the best of my ability. I confirm that the consent has been given voluntarily and free of coercion. A copy of this form has been given to the participant.

Print Name of Researcher _____

Signature of Researcher _____

Date _____

Appendix D

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF

PROTOCOL ASSESSORS MEETING

Candidate Full Name: SANELISIWE BAKISIWE ZETHU BACFOUR

Student Number: 1928755 Date: 19/6/2018

School / Department / Division: PAEDIATRICS (MMED PAEDS)

1. **Type of study** *(tick all that apply)*:
   - ✓ Quantitative
   - o Qualitative
   - o Mixed Methods
   - o Laboratory
   - o Clinical
   - o Other, please specify.....

2. **Is title of the study appropriate** (*preferably fewer than 20 words*)? Yes ✓ / No

Comments: _____

3. **Are the study objectives clear and linked to the research aim and title?** Yes ✓ / No

Comments: _____

4. **Is the design of the study appropriate to meet the study objectives?** Yes ✓ / No

Comments: _____

03/03/2016

Overall recommendation regarding the protocol:

i. Revision of the protocol to the satisfaction of the Supervisor (**NB: if HoD approval is also required, please specify**): Yes / No
*(**Candidate**: one copy, list of corrections with page numbers and Supervisor approval letter – submit to PG Office).*

ii. Revision of the protocol to the satisfaction of the Assessor Group/Chair: Yes / No
*(**Candidate**: one copy, list of corrections with page numbers, Supervisor approval letter – submit to PG Office and PG Office to forward to the Assessor Group Chair).*

iii. Revision of the protocol and resubmission of the revised protocol to the next Assessor Group Meeting: Yes / No
*(**Candidate**: six copies, list of corrections with page numbers, Supervisor approval letter – submit one copy to PG Office / 5 to school assessor group administrator / for PhD, all six copies to be submitted to the PG Office).*

iv. Candidate goes ahead (*no revision required*): Yes / No

Details of Assessors:

Name:	Email:	Sign:
D S MACKINNON	diane.leask@wits.ac.za	
L. SEPENG	Letlhogonolo.Sepeng@wits.ac.za	

Details of Assessor Group Chair:

Name:	Email:	Sign:
John Rodda		

Date: 19/6/2015

Appendix E

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 30th May 2018

TITLE OF PROJECT:

The Incidence and outcomes of acute kidney injury in critically-ill neonates.

UNIVERSITY: Witwatersrand

Principal Investigator: Dr SBZ. Balfour

Department: Paediatrics

Supervisor : Dr K L Petersen

Permission Head Department (where research conducted): Yes

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

Recommended
(On behalf of the MAC)
Date: 30/05/2018

Approved/Not Approved
Hospital Management
Date: 04/06/18

Appendix F

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Sanelisiwe Balfour

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180724

NAME: (Principal Investigator)	Dr Sanelisiwe Balfour
DEPARTMENT:	School of Clinical Medicine Department of Paediatrics Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	The incidence and outcomes of acute kidney injury in critically-ill neonates at Chris Hani Baragwanath Academic Hospital: a prospective descriptive study
DATE CONSIDERED:	27/07/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Karen Petersen and Dr Letlhogonolo Sepeng
APPROVED BY:	Dr C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	15/05/2019

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed July and will therefore be due in the month of July each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature — Date: 21/05/2019

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix G (Turn It In Report)

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