Prevalence of Acute Kidney Injury in the Paediatric Intensive Care Unit at Pelonomi Regional Hospital

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A research report submitted to the Faculty of Health Sciences, University of the Free State, in fulfilment of the requirements for the degree of Masters of Medicine in the branch of Paediatrics.

Bloemfontein 2017

… "Education is not the learning of fact, but the training of the mind to think."

Albert Einstein (1879-1955)

Declaration

I, Marelize Reynders declare that this research report is of my own work. It is being submitted for the degree of Masters of Medicine in the branch of Paediatrics at the University of the Free State, Bloemfontein. It has not been submitted before for any degree or examination at this or any other institution.

8th day of December 2017

Abstract

Background

Acute kidney injury (AKI) is common in critically ill children and associated with an increased mortality rate. This study aimed to determine the prevalence of AKI in critically ill children admitted to the paediatric intensive care unit at Pelonomi Hospital, the most common admission diagnoses among these patients admitted with AKI and the mortality rate in this cohort.

Method

A retrospective observational study design was followed. The study milieu was a 5-bed tertiary paediatric intensive care unit at Pelonomi Hospital in Bloemfontein. All patients between one month and thirteen years old admitted to the paediatric intensive care unit for the period 1 January 2015 to 31 December 2015 were screened for AKI. The clinical and laboratory features of the included children were recorded and used to diagnose AKI utilizing both the serum creatinine and urine output criteria of the paediatric Risk, Injury, Failure, End-stage and Failure classification (pRIFLE).

Results

The clinical records of 245 patients were evaluated, of these, 35 had to be excluded. Acute kidney injury was found in 108 (51.4%) of the remaining 210 patients. Of these 108 patients with AKI, 32 (29.6%) patients reached pRIFLE maximum of Risk, 30 (27.7%) patients reached Injury, and 46 (42.5%) had Failure. The most common admission diagnoses in children with AKI were pneumonia (30.5%) and acute diarrhoeal disease (16.7%). A total of 30 (14.2%) deaths occurred during the study period and AKI was present in 20 (18.5%) of these deaths.

Conclusion

Acute kidney injury is common in the paediatric intensive care. The most common admission diagnoses of the children found to have AKI were infective diseases like pneumonia and acute diarrhoea. Critically ill children have an increased risk for mortality.

Dedication

I would like to dedicate this research report to the Lord my Saviour as well as my family, especially my grandfather Jan Hendrik Lombaard.

Acknowledgements

With appreciation and thanks to:

1. Dr. M Jonas, consultant of the Paediatric Intensive Care unit of Pelonomi Hospital, Bloemfontein
2. Mr. C van Rooyen and the Department of Biostatistics at the University of the Free State
3. Pelonomi Hospital records department
4. Department of Paediatrics and Child Health at the University of the Free State
5. Free State Department of Health

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Acronyms and Abbreviations

AKI	Acute Kidney Injury
AKI-EPI	Acute kidney injury epidemiology study
AKIN	Acute Kidney Injury Network
ARF	Acute Renal Failure
AWARE	Assessment of World Acute kidney injury, Renal angina and Epidemiology
Cr	Creatinine
eGFR	Estimated glomerular filtration rate
GFR	Glomerular filtration rate
ICU	Intensive care unit
IL-18	Interleukin-18
KDIGO	Kidney Disease Improving Global Outcomes
KIM-1	Kidney injury molecule-1
LOS	Length of stay
NGAL	Neutrophil gelatinase-associated lipocalin
NHLS	National Health Laboratory Services
PICU	Paediatric intensive care unit
pRIFLE	Paediatric RIFLE classification
RAI	Renal angina index
RIFLE	Risk, Injury, Failure, Loss, End-stage
RRT	Renal replacement therapy

Chapter 1 Introduction and Literature Review

1.1 Introduction

Acute kidney injury (AKI) has replaced the term acute renal failure consequently describing a continuum of disease rather than a solitary incident, while also attempting to standardize the definition.[1-3] This disease is characterized by a decrease in the glomerular filtration rate precipitating a rise in blood nitrous waste products (mostly creatinine and urea) and deranged fluid and electrolyte homeostasis.[1,3] Acute kidney injury increases the risk of mortality in critically ill patients.[1]

Although modern renal replacement therapies have developed to manage many of the complications of AKI successfully, AKI continues to be associated with a high mortality in critically ill patients.[4-10] This is especially true in the paediatric intensive care unit (PICU). Research has shown that the high mortality rate can be attributed to four major factors. Firstly, the interaction between AKI and multi-organ dysfunction (so called organ cross-talk) leading to a potentially fatal vicious cycle.[11] Secondly, due to the importance of the kidney in pharmacokinetics, failure of function contributes to medication failure and an increased risk for medication related adverse effects.[12] Acute kidney injury can also be precipitated by some of the medications used in the PICU. These effects are caused by impaired protein binding, reduced drug metabolism and finally decreased renal clearance.[12] Thirdly, AKI compromises the immune function thus increasing susceptibility to infection.[11] Finally AKI gives rise to fluid overload which is a known independent variable for mortality.[13-14]

Research from developed as well as developing countries highlights the increasing prevalence of AKI in children, with the prevalence in critically ill children ranging from as low as 5% to as high as 82%.[6,9,10,14,16-20] Factors like ignorance, poverty, lack of access to medical care, geographic location, age, illness severity and seasonal variation are responsible for this wide range.[2,8,21] Unfortunately most of the data originates from developed countries with very little sub-Saharan African statistics available.[6,7,22,23]

The cause of AKI in the ICU setting is usually multifactorial.[6] Risk factors such as hypotension, hypovolemia, sepsis, liver failure, cardiac failure and ingestion of toxins or medications are present in many of the patients admitted to PICU.[6,24] In developing countries the prevalence of AKI was highest in infants and males.[18,20] Data from the recent global snapshot by the International Society of Nephrology identified community-acquired causes of AKI to be most prevalent in lower-middle-income countries and hospital acquired AKI more common in high-income countries.[22] Primary renal conditions like glomerulonephritis and nephrotic syndrome were major contributors to AKI in other African countries, with febrile diseases a close second.[18,25] An estimated 30% of reported AKI cases were avoidable.[26]

Acute kidney injury negatively influences both short term and long-term outcomes in PICU. Even mild cases of AKI are associated with an increased need for renal replacement therapy, as well as an increased risk for developing chronic renal disease.[7,8,14] Renal replacement therapy was reportedly needed in 5.8% of AKI cases in a PICU in India.[20] Critically ill children with AKI have longer ICU stays and a prolonged need for mechanical ventilation.[8-9,14,17-21]

The 0by25 investigation found that 10% of patients diagnosed with AKI had residual renal dysfunction at the point of discharge.[22] A significantly higher mortality rate ranging from 12-50% is reported in critically ill children with AKI.[5,6,7,20]

There are still many obstacles regarding the management and care of critically ill children with AKI. Access to care is still a substantial problem.[7,20-21,27] Poor access to healthcare leads to a delay in admission and diagnosis of patients with AKI, contributing to a higher AKI stage.[7] Many patients are also lost to follow up due to a low rate of reporting.[7] Survival is not only dependent on the cause of AKI, but also the availability of treatment and follow up care.[2] All of the aforementioned factors lead to a poor outcome. Initiating therapeutic intervention before loss of function is critical to improving results.[14]

One can only improve the understanding and subsequently the outcome of AKI once the burden is quantified. This study therefore aims to determine a verifiable reflection of the prevalence of AKI in the PICU population of Pelonomi Hospital in Bloemfontein. Secondly to identify the most common admission diagnoses of children also found to have AKI during their admission in PICU, and lastly, to determine the mortality rate of these patients. Greater awareness of AKI would decrease avoidable causes, improve outcomes and improve the follow up rate of these patients.

1.2 Literature Review

In order to pursue research in the field of acute kidney injury some critical concepts must be understood. This literature review will attempt to address the following:

1. Definition and classification of AKI
2. Diagnostic workup of AKI
3. Recent global research

1.2.1 Definition and classification of Acute Kidney Injury

Comparison with earlier research is hampered by the fact that more than 35 definitions of acute renal failure existed previously. In 2004 the Acute Dialysis Quality Initiative proposed the Risk, Injury, Failure, Loss, End-stage (RIFLE) criteria that uses the change in serum creatinine (sCr) from baseline and urine output to classify AKI.[28] The RIFLE criteria was further adapted to the paediatric population (pRIFLE) by replacing the change in serum creatinine in the definition, with a change in an estimated creatinine clearance as calculated by the Schwartz formula (Table 1).[2,3] Severe AKI according to

pRIFLE is defined as a decrease in eCCl of 50% or more from baseline or urine output of <0.5ml/kg/h for >16hours. The pRIFLE criteria classifies three stages (risk, injury and failure) and provides two outcomes (loss of function and end-stage).

Table 1: pRIFLE definition and classification of AKI

Classification	Estimated Creatine Clearance Criteria	Urine output Criteria
Risk	Decrease of eCCl* by 25% from baseline	<0.5ml/kg/h for 8hours
Injury	Decrease of eCCl* by 50% from baseline	<0.5ml/kg/h for 16hours
Failure	Decrease of eCCl* by 75% from baseline	<0.3ml/kg/h for 24hours **or** anuric for 12hours
Loss	Loss of renal function for more than 4 weeks	
End-stage	End stage renal disease	

*eCCl calculated by the Schwartz formula

Subsequent research revealed that even small changes in creatinine were associated with a higher mortality risk. The Acute Kidney Injury Network (AKIN) acknowledged this by modifying the RIFLE criteria in 2007 to improve the sensitivity of the guidelines for AKI diagnosis (Table 2).[23] In 2012 both the previous classifications were combined resulting in the Kidney Disease Improving Global Outcomes (KDIGO) classification (Table 3).[29] The maximum change in serum creatinine or urine output defines the stage of AKI. Severe AKI is classified as stage 2 or 3 according to the AKIN or KDIGO criteria and Injury or Failure as specified by the pRIFLE classification. Chronic kidney disease is defined as persisting kidney disease for more than 90days.[28-29] The risk of adverse outcomes is greatest when both serum creatinine and urine output criteria are met.[29]

Table 2: AKIN definition and classification of AKI

Classification	Serum Creatinine Criteria	Urine Output Criteria
Stage 1	Increase in sCr to 1.5 times from baseline **or** increase in sCr >0.3mg/dl	<0.5ml/kg/h for 6hours
Stage 2	Increase in sCr to 2 times from baseline	<0.5ml/kg/h for 12hours
Stage 3	Increase in sCr to 3 times from baseline **or** increase in sCr >4mg/dl	<0.3ml/kg/h for 24hours **or** anuria for 12hours

Table 3: KDIGO definition and classification of AKI

Classification	Serum Creatinine Criteria	Urine Output Criteria
Stage 1	Increase in sCr to 1.5-1.9 times from baseline **or** Increase in sCR >0.3mg/dl	Urine output <0.5ml/kg/h for 6-12h
Stage 2	Increase in sCr to 2.0-2.9 times from baseline	Urine output <0.5ml/kg/h for >12hours
Stage 3	Increase in sCr more than 3 times from baseline **or** serum creatinine >4.0mg/dl **or** treatment with renal replacement therapy **or** in patients <18years, decrease in estimated glomerular filtration rate (eGFR) to <35ml/min/1.73m^2	Urine output <0.3ml/kg/h for >24hours **or** Anuria for >12hours

Diagnostic criteria for AKI according to KDIGO:

1. Increase in serum creatinine by >0.3mg/dl
2. Increase in serum creatinine by 1.5 times baseline, which is known or presumed within 7 days prior
3. Urine volume <0.5ml/kg/h for 6hours

All three classifications have been validated for use in paediatrics.[2, 6, 9 ,16, 29] This begs the question whether there is one classification that is superior to the others. Sutherland et al (2015) found that the incidence of AKI in their cohort to be 51.1% using pRIFLE, 37.3% according to AKIN and 40.3% utilizing the KDIGO criteria.[16] Inconsistency was most prominent in the stage 1 group, with the pRIFLE classification being the most sensitive and classifying more patients as risk/stage 1.[16] The pRIFLE and KDIGO definitions corresponded 87.3% regarding the diagnosis of AKI while agreeing 84.2% of the time on the staging.[16] There is however no general consensus as to which definition is supreme.[16,30]

1.2.2 Diagnostic workup of AKI

1.2.2.1 Serum Creatinine

Creatinine is the end metabolite of creatine metabolism.[14, 24, 31] Serum creatinine is not kidney specific and there are thus some limitations in the use of creatinine-based criteria for AKI. Serum creatinine and urine output are only markers of renal excretory function and do not provide information on any

of the other vital roles of the kidney, i.e. immunological or endocrine functions.[24, 31] Creatinine production is determined by three factors:

1. Amount of ingested creatine (intake of red meat)
2. Muscle function
3. Amount of creatine generated in the liver, pancreas and kidney

Normally creatinine is produced at a constant rate and the production rate is matched by the renal clearance rate because it is freely filtered by the glomeruli.[31] Serum creatinine as a functional marker for AKI is not flawless due to the following[3, 31-32]

1. Normal creatinine half-life of 4 hours increases to as much as 72 hours if the glomerular filtration rate decreases
2. Healthy kidneys have a large functional reserve and serum creatinine will only rise after 25-50% of kidney function has already been lost
3. Serum creatinine values can be influenced by non-renal factors like muscle mass, hydration status, gender, age, diet, sepsis and liver disease
4. Creatinine is dialyzable

Table 4: Possible drawbacks of AKI diagnosis using creatinine and urine output

Scenario	**Effect**
Reduced creatinine production	Delayed or missed AKI diagnosis
Obesity	Over diagnosis (weight based urine output)
Progressive chronic renal disease	Misdiagnosis of AKI
Fluid resuscitation or fluid overload	Delayed diagnosis due to dilution effect
Medication interfering with tubular creatinine secretion (i.e. cimetidine, trimethoprim)	Misdiagnosis (rise in serum creatinine without AKI)
Extrinsic creatinine administration (used as a buffer in some medication like dexamethasone)	Pseudo-AKI

1.2.2.2 Urine output

Urine output is one of the oldest clinical indicators of renal injury, but is restricted by poor specificity.[33] This problem is confounded by the fact that urine output is not only part of the diagnostic criteria, but is also an endpoint of the disease. Potential pitfalls are as follows: [31 ,33]

1. Accurate measurement of urine output is often not possible in incontinent or uncooperative children in which case bladder catheterization is necessary.

2. Weight-based calculations of urine output may be deceptive in obese patients and can lead to an overestimation of AKI

3. Normal or increased urine output does not rule out AKI. It may be present in patients with polyuric AKI e.g. with vancomycin and aminoglycoside toxicity.

4. Urine production rate is also a function of anti-diuretic hormone and might be decreased as an appropriate physiological response to hypovolemia, post-surgery or trauma and following stress or pain, in the absence of AKI

1.2.2.3. Estimated glomerular filtration rate

The glomerular filtration rate (GFR) is viewed as the best indicator of function in a healthy as well as a diseased kidney.[34] Determining the true GFR is complex and costly to perform routinely.[35-36] Glomerular filtration estimation calculations provide a cheap and non-invasive alternative.[35] Since 2002 the National Kidney Foundation Kidney Disease Outcomes Quality Initiative recommended the use of proposed formulas by Schwartz et al. (1976) and Counahan-Barratt et al. (1976) for calculating estimated GFR (eGFR).[35,37]

After the Schwartz formula had come into practice, the method of creatinine measurement from the Jaffe method to more precise enzymatic assays. Measurement of serum creatinine using the new assays resulted in overestimation of eGF and underestimation of AKI.[38] This particular problem was addressed by Schwartz et al in 2009 by developing a new GFR estimation equation.[38] The author provided an updated bedside formula as eGFR = [0.413 x height (cm)]/serum creatinine (mg/dl). Again, this calculation is not without opposing arguments as the study was conducted mainly in children with chronic kidney disease. Subsequent research proved the modified bedside Schwartz formula to be valuable even in children with near normal kidney function.[36-37] The Schwartz formula coefficient however does not correct for age and gender related patient differences, but comparisons in other studies have found that these variables do not significantly impact on the result in the pre-teen population .[37-38]

Multi-marker equations for the calculation of eGFR are more sensitive and accurate, but due to their complexity they are not suited for bedside use. A selected group of children however need precise GFR measurement as the creatinine concentration itself might be inaccurate.[37] These are children with conditions like body deformities and malnutrition.[37]

1.2.2.4 Baseline Creatinine

The definition in all three of the above described classifications requires a change from the baseline creatinine. The baseline creatinine is defined as the lowest serum creatinine in the preceding 3 months for the pRIFLE criteria, 7days for the KDIGO criteria and 48hours for the AKIN criteria. [23, 28,

[29] It becomes a dilemma if a patient has no baseline creatinine. A presumed baseline eGFR level of 120ml/min/1.73m^2 has been validated for use where there is no previous recorded eGFR.[5,28,29] There is an inherent problem with the AKIN criteria as it does not make use of an eGFR in the definition of AKI. The KDIGO criteria only includes an eGFR in stage 3 kidney disease.[28,29] The problem therefore with the AKIN and KDIGO classifications is when no baseline creatinine is known, the early stages of AKI are overlooked, resulting in delayed diagnosis of AKI. Preventative strategies cannot be implemented if the early signs of AKI are not identified on admission. An average serum creatinine for gender and age, specific to the laboratory for the institution, was used by Alkandari et al (2011), but this method has not been validated in other studies.[19]

1.2.2.5 Other indicators of AKI

Biomarkers of AKI appear in response to tubular cell injury and are measured in serum as well as urine samples.[2,10,14] Evaluation of real time kidney function impairment is not possible with the known indicators (serum creatinine and urine output), but the use of novel biomarkers might improve the picture. The most promising biomarkers currently being researched are: plasma and urine neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, interleukin-18 (IL-18) and kidney injury molecule-1 (KIM-1).[2,10] Plasma and urinary NGAL rises within hours in patients who develop AKI and has been studied in post-cardiac surgery and septic shock patients as a predictor of AKI. [2,3]Although the results from studies where biomarkers were used promising, they are not commercially available in the South African public sector yet.

A recent concept aimed at improving prediction of AKI in critically ill children, is termed as the renal angina index (RAI).[3,32] This index uses the patients' demographic data, clinical indicators and laboratory measurements at the time of admission to predict the risk of developing AKI within the next 72 hours.[32] Recent studies found that a RAI score >8 had a significant negative predictive value of >95%.[32] It was also reported that patients with indicators meeting the renal angina criteria were more likely to double their baseline serum creatine in the next 72 hours.[32] The RAI score is used as a screening tool to predict the risk of AKI in critically ill children. It is not diagnostic of AKI.

1.2.3 Global research

Three large prospective multicentre studies have contributed to the body of knowledge regarding AKI epidemiology. Hoste et al (2015) launched the AKI-EPI study, prospectively investigating the incidence and outcomes of AKI in both adult and paediatric ICU patients.[9] Patients from 97 centres across North America, Europe, Asia and Australia formed the study population.[9] Although the AWARE study investigators made use of patients from the same countries as used by the AKI-EPI group, they only included critically ill children from 32 paediatric intensive care units.[8] The International Society for Nephrology launched the "Zero preventable deaths" (0by25) research project and included AKI cases (again adults and children) from 289 centres in 72 countries across six continents.[22] Acute

kidney injury was defined using the KDIGO criteria in all three projects. The AKI-EPI group reported an AKI incidence of 57.3%, while the AWARE study only reported a 26.9% incidence.[8-9] The 0by25 group found that 58% of AKI cases were community acquired and that 80% of the patients were from lower-middle-income countries.[8] This group also sited hypotension and dehydration as the most common causes for AKI.[8]

The mortality rate was the most frequent outcome measured. The AWARE investigators reported a mortality rate of 3.4% while 0by25 group reported a much higher rate of 11%.[8, 22] All three studies concur that a higher AKI stage is associated with an increased risk of mortality.[8, 9, 22]

Although the mentioned studies have a prospective study design, there are some shortcomings. Causal relation cannot be determined due to the observational study design. Both the AKI-EPI and 0by25 studies included adults in the study population. This poses a problem as adults have chronic coexisting conditions that are associated with an increased risk for AKI and mortality, and that may lead to biased results as children generally do not have chronic comorbidities. Another limitation in the AKI-EPI study as well as the AWARE study is that the participants were mostly from first world countries and no patients from African countries were included. Developing countries usually have poor availability of resources and inadequate healthcare infrastructure leading to delayed diagnosis and increased risk for loss of life. Only the AWARE study identified the baseline eGFR for the definition and assigned a value of 120ml/min/1.73m^2 in cases where no baseline was known. Acute kidney injury incidence in the AWARE study might also be misrepresented as the study could not compensate for seasonal variation due to a short study duration of only three months.

Research done in Africa by Esezobor et al (2012) and Antwi et al (2015) differs from the multinational studies by rather using a retrospective observational study design and pRIFLE as the AKI definition. Esezobor et al (2012) reported an AKI prevalence of 17.4% while Antwi et al (2015) only found a 1.3% prevalence. Both authors reported a male predominance and attributed primary renal disease as the main aetiological factor.[18,39] Esezobor et al (2012) found a mortality rate of 28.4% and Antwi et al (2015) a 20.9% mortality rate.[18,39] The surprisingly high mortality rate found by Antwi et al (2015) is most likely skewed by severity of the disease as 72% of the mortality cases in this study with AKI required renal replacement therapy.[39] Due to the lack of dialysis service these patients did not receive any renal replacement therapy.[39]

Both studies are limited by their retrospective nature as well as the single centre basis of the studies. Patients in both studies were sourced from nephrology units which might contribute to diagnosis bias and might explain why primary renal disease was found to be the main cause of AKI.

In summary the reported prevalence, aetiological factors and mortality rate of AKI vary considerably. The epidemiology of AKI in critically ill children is inadequately described. Many variables in lower-middle-income countries contribute to the mortality rate, but it is accepted that children with AKI in PICU have a higher risk of death. Due to the inconsistent reports on the prevalence, etiology and

mortality rate of AKI in the paediatric intensive care units in middle income countries, research on the occurrence of acute kidney injury and its implications in the local paediatric intensive care population is essential. This is then the main objective of this study.

Chapter 2 Study Objectives, Concept Clarification and Definitions

2.1 Research question

The research question for this study was: What is the prevalence of acute kidney injury in patients admitted to the paediatric intensive care unit of Pelonomi Hospital.

2.2 Research aim and objectives

The primary aim/objective of the research was to determine the prevalence of acute kidney injury in patients admitted to the paediatric intensive care unit of Pelonomi Hospital for the period of January 2015 to December 2015.

A second objective was to identify the most common primary diagnoses on admission to the paediatric intensive care unit in patients who had acute kidney injury. The third and last objective of the study was to determine the mortality rate among patients with acute kidney injury in the paediatric intensive care unit.

2.3 Concept clarification and definitions

Acute kidney injury was defined using the pRIFLE criteria. The estimated creatinine clearance was calculated using the modified bedside Schwartz formula (eCCl = k x [height/serum creatinine] with height expressed in centimetres and serum creatinine in mg/gL). The factor used in the equation was dependant on the age of the patient (<6months k=0.25, 6-9months k=0.35, 9-12months k=0.35 and >12months k=0.4). AKI is accordingly defined as decrease in eGFR of more than 25% from baseline or a recorded urine output of less than 0.5ml/kg/h for a period of 8hours.

Patients were classified according to the pRIFLE criteria as risk, injury or failure based on their calculated estimated creatinine clearance and urine output. The baseline eGFR used in this study was a recorded serum creatinine within 3 months prior to admission to PICU. If no baseline serum creatinine was available, a baseline eCCl of 120ml/min/1.73m^2 was assumed. This assumption was based on previous research which showed that a GFR of 120ml/min/1.73m^2 was a more accurate reflection of a normal renal function in children rather than the previous suggested value of 80ml/min/1.73m^2.[1-2,5,20,34,37]

Table 5: pRIFLE classification for this project

Classification	Estimated creatine clearance Criteria	Urine output Criteria
Risk	Decrease of eCCl* by 25% from baseline	<0.5ml/kg/h for 8hours
Injury	Decrease of eCCl* by 50% from baseline	<0.5ml/kg/h for 16hour
Failure	Decrease of eCCl* by 75% from baseline	<0.3ml/kg/h for 24hours **or** anuric for 12hours

*eCCl calculated by the modified bedside Schwartz formula

Oliguria was defined as a urine output of 0.1-0.5ml/kg/h while polyuria was defined as a urine output of more than 5ml/kg/h. Hypernatermia was recorded when a serum sodium concentration was more than 150mmol/l and hyponatremia when the serum sodium concentration was less that 130mmol/l. Hyperkalemia was noted as a serum potassium concentration of more than 6.0mmol/l. Hypertension was defined as a systolic or diastolic blood pressure greater than the 95th centile for age, gender and height using the normogram published in the fourth report of the National High Blood Pressure Education Group.[40] Sepsis was defined as a systemic inflammatory response due to suspected or proven infection. Systemic inflammatory response was assumed in the presence of a measured white cell count of >12 x 10/mm^3 at presentation and a peripheral temperature of >38°C persisting for more than 24hours after presentation.[41] Tachycardia and tachypnoea were not included as this was a retrospective review of patient files and an objective assessment of these variables and their relation to sepsis could not be made. Metabolic acidosis was defined as a serum pH of <7.35 on a blood gas sample with severe metabolic acidosis as a pH of <7.0.

Chapter 3 Material and Methods

3.1 Study design

A retrospective observational cross-sectional study design was chosen due to financial and timing constraints. It is noteworthy that most researchers in developing countries used a retrospective study design, which might be explained by resource constraints, including both workforce and research funding constraints.[18,20,40]

3.2 Study setting

Pelonomi Hospital is a tertiary hospital situated in Heidedal in Bloemfontein. It is a 758-bed hospital with 74 general paediatric beds and 30 surgical beds used by paediatric surgery, orthopaedic surgery and neurosurgery. Four beds are also reserved for children in the burns unit at Pelonomi Hospital.

This tertiary hospital serves as a drainage centre for the Central and Southern Free State area. Pelonomi Hospital receives patients from local primary health care centres in and around Bloemfontein, as well as referrals from district and regional hospitals in the abovementioned drainage area. It is also the referral hospital for all trauma and burns cases from the entire Free State. The general paediatric unit does not include specialised paediatric services like nephrology, neurology, cardiology and pulmonology, as these patients are treated at Universitas Academic Hospital, also situated in Bloemfontein.

The 5-bed paediatric intensive care unit at Pelonomi admits patients from general paediatrics, paediatric surgery (including children with burns), Pelonomi casualty, Pelonomi trauma unit as well as children managed by neurosurgery and orthopaedic surgery. Children from neonatal age up to 13years old are admitted to the paediatric intensive care unit.

3.3 Study population

3.3.1 Inclusion criteria

All patients admitted to the paediatric intensive care unit at Pelonomi Hospital who were older than 30days and less than 13years old, during the period from 1 January 2015 to 31 December 2015, were eligible for inclusion in the study. Every repeat admission to PICU was counted as a separate event. The paediatric intensive care unit admits patients from neonatal age (0-28 days) up to children aged 12 years (not having turned 13).

3.3.2 Exclusion criteria

A patient was excluded from the study if any of the following was true:

1. Age less than 30days
2. Age more than 13years
3. Patients with known chronic kidney disease
4. Patients admitted for less than 24hours after elective surgery for observation
5. Patients with incomplete records or without a measured length

Infants were excluded for the following reasons:

- The definitions according to serum creatinine could not be used in this group as maternal creatinine is known to cross the placental barrier.[32] In the first few days after birth the serum creatinine of a neonate is a reflection of the mother's renal function. It can therefore not be used to diagnose AKI in a neonate (definitely not on day one). Sequential serum creatinine levels in combination with urine output are necessary to diagnose AKI in this population.[32]
- Term, as well as premature infants, have a low GFR with a wide distribution of creatinine values complicating the diagnosis of AKI.[42]
- Higher serum bilirubin levels which may be present in the first week of life may with Jaffe endpoint measurement of serum creatinine levels and result in falsely elevated serum creatinine.[42]

Patients older than 13years were also excluded mainly due to two reasons. Firstly, as per admission protocol for Pelonomi PICU these patients were usually not admitted to PICU, but rather referred to adult medicine. Secondly these patients again posed a dilemma in the diagnosis of AKI using pRIFLE, as puberty induces changes in the main body composition between boys and girls.[36-37] Use of an adolescent model where an interaction term between gender and height/serum creatinine ratio was incorporated, might have addressed this issue, but again would complicate the collection process.[36]

Chronic renal failure patients were also excluded. In patients with CKD, changes in serum creatinine depict variable GFR changes, and larger changes in serum creatinine might then actually be within the acceptable daily variation.[31] Creatinine is dialyzable and patients with chronic kidney disease were more likely to be dialyzed.[32,33] Including chronic kidney disease might have caused a skewed result due to misdiagnosis.

Patients admitted for post-operative observation that stayed in PICU less that 24hours, were deemed healthy passers-by who did not necessitate blood sampling. These patients were excluded.

Patients were excluded from the study if their patient records could not be found or if the information in the files was incomplete. Patients without a measured urine output were not excluded and classified as AKI using only their serum creatinine values.

3.4 Measurement

The collection process started by identifying the hospital numbers for patients admitted to PICU for the set period. The hospital numbers were obtained from the PICU admission record books for January 2015 to December 2015. Data was mainly captured from three sources: the MEDITECH discharge summary of each patient, hard copy patient file and the National Health Laboratories Service TrakCare web results viewer. Each of the patients admitted to PICU were expected to have a MEDITECH discharge summary. Each summary would include the following:

1. Demographic information: Age, gender, residing town

2. Referring discipline

3. ICD 10 diagnosis
4. Complete paediatric history
5. Anthropometry
6. Admission examination
7. Relevant special investigations
8. Summary of ICU management/stay
9. Discharge plan

The patient file was reviewed to capture information that was not recorded in the discharge summary. The required blood results (serum creatinine, serum urea, serum sodium, serum potassium, white cell count) were obtained from the National Health Laboratories Service TrakCare web results viewer.

1. Each admission in the stipulated period was evaluated for inclusion. A data form (Appendix A) was completed for each patient included in the study. Only the reason for exclusion was noted for those not included. The following information was recorded on the data form:
2. Demographic data
3. Weight and length as anthropometry
4. Referring discipline
5. ICD 10 Diagnosis primary and secondary diagnoses
6. Length of stay
7. Blood results: serum creatinine, urea, sodium, potassium
8. Blood gas results
9. Urine output classification
10. pRIFLE classification
11. Presence of sepsis, hypertension and multi-organ failure
12. Use of continuous positive airway pressure (CPAP), invasive mechanical ventilation, peritoneal dialysis, haemodialysis
13. Outcome: discharge or death

The admission serum creatinine and the highest serum creatinine recorded during admission to PICU were captured. The biochemistry and blood gas results on the day when the peak serum creatinine was measured, was recorded. The number of days in PICU (day of admission is day1) when the serum creatinine had reached its peak, was also recorded. These serum creatinine values were then used to calculate the eCCl using the modified bedside Schwartz formula. The lowest eCCl and documented urine output was used to classify AKI according to the pRIFLE criteria and recorded on the data form. Patient files was reviewed for the severity of metabolic acidosis, presence of hypertension, sepsis and use of inotropic agents. The number of days patients required respiratory support such as continuous positive airway pressure or invasive mechanical ventilation were also recorded. The need for dialysis (haemodialysis or peritoneal dialysis) and main outcome either as discharge from PICU or death, was documented. The collected data was transferred onto an Excel spreadsheet and submitted for biostatistical analysis.

3.5 Statistical analysis

Statistical analysis was performed by the Department of Biostatistics at the University of the Free State. Continuous variables were expressed as means or medians as appropriate, while categorical data was presented as percentages. The prevalence of acute kidney injury was calculated as the total number of AKI episodes during the study period divided by the total number of patients admitted to the paediatric intensive care unit between the age of one month and 13 years.

3.6 Pilot study

A pilot study was conducted with the following objectives in mind:

1. To evaluate the appropriateness of the data form
2. MEDITECH as a source of information
3. Assessing for problems related to time needed for data collection.

The first 20 patients admitted to Pelonomi PICU in 2015 were used as the pilot study population. These patients were evaluated for inclusion using the exact same criteria as for the main study. The same procedure of data collection, recording and analysis were followed as was planned for the main study. Statistical analysis was done as explained above. The pilot group had a 65% prevalence of AKI with pneumonia being the most common diagnosis.

The data form generally performed well, but a single adjustment was made. The option of no catheter was added to question 15 regarding urine output. The MEDITECH database was adequate to collect most of the data needed on the data form except for evaluation of metabolic acidosis as blood gas analysis were almost never noted in the special investigations section. This information was then

sought in the patient file. Information of anthropometry of patients was not documented in their discharge summaries and had to be retrieved from their admission books. Data collection proceeded swiftly due to the efficiency of the MEDITECH database and NHLS Trakcare web results viewer. All the patients in the pilot study were also included in the main study.

3.7 Ethical aspects

The head of the Department of Paediatrics at the University of the Free State gave permission to perform the study. Consent for the use of patient files, MEDITECH database and the NHLS TrakCare web results viewer was obtained from the clinical manager of Pelonomi Hospital. Ethics approval was obtained from the Ethics Committee of the Faculty of Health Sciences at the University of the Free State (Appendix B) with ethics approval number HSREC 194/2016(UFS-HSD2016/1510). The project was also registered and approved by the Free State Department of Health with study number FS2017RP44263.

In terms of confidentiality each patient included in the study was assigned a study number as used on the data form. No identification information was collected on the data form. The data was collected by the investigator only. No personal/identification information was shared with any third party and will not be unless required so by law.

Chapter 4 Results

4.1 Study population

Over a period of 11 months 245 cases were admitted to the paediatric intensive care unit at Pelonomi Hospital. Thirty five (14.3%) patients were excluded (Figure 1). An additional unknown number of patients who were admitted in December 2015, were also excluded due to lost patient documentation. Four patients were admitted twice (accounted for 8 admission) during the 11month period. Acute kidney injury was recorded in only one of these patients, while no mortalities were recorded. Of the remaining 210/245 (85.7%) admissions, AKI was diagnosed on 108/210 (51.4%) occasions. The most common reason for exclusion was due to an age of less than thirty days. Notably all 6 patients excluded for the absence of a recorded length were referred from surgical disciplines.

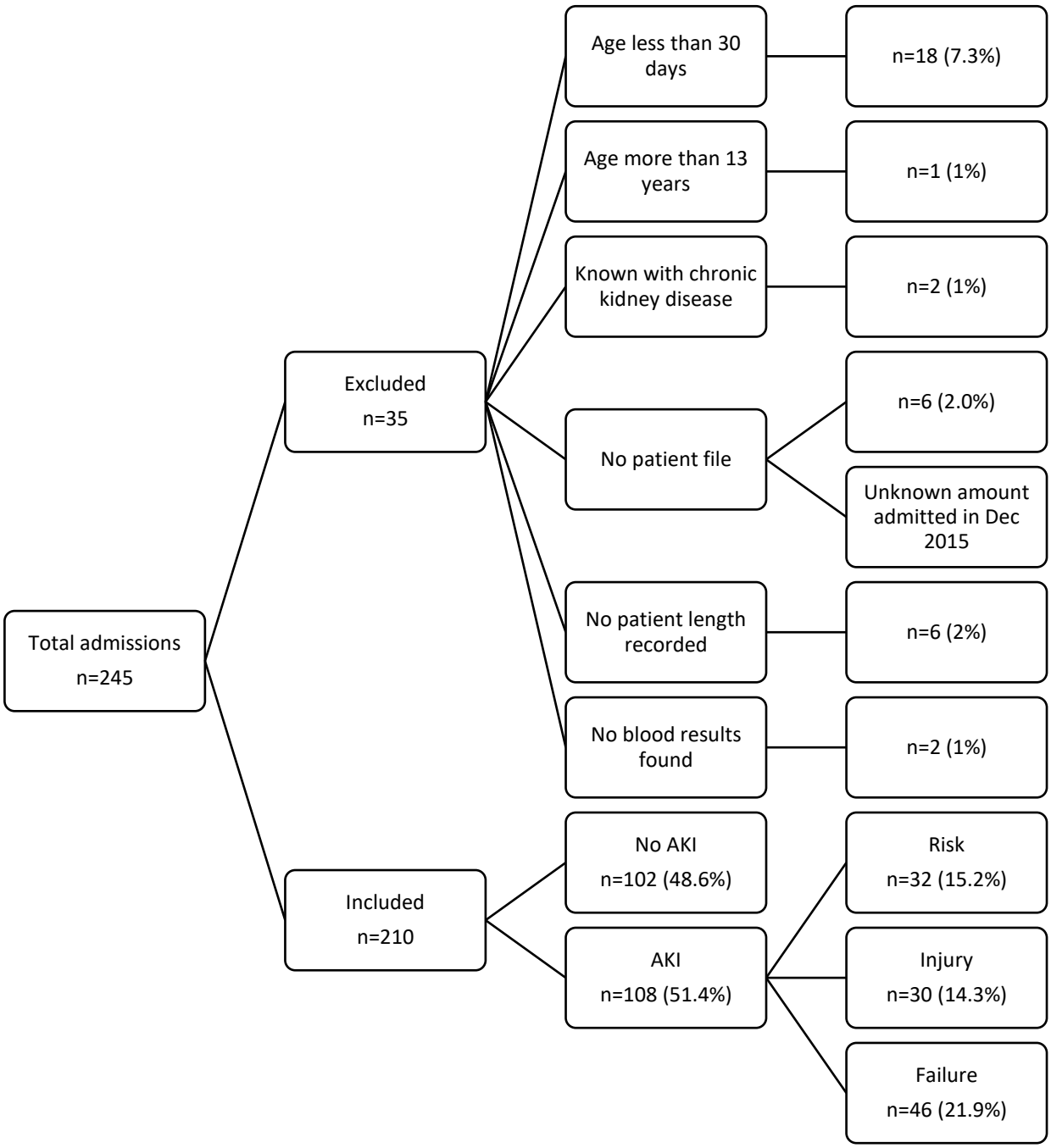

Figure 1: Flow diagram depicting patients admitted to PICU, excluded patients, reason for exclusion and patients included in the study

4.2 Demographic profile

The median age for the study population was 8 months (range 1 month to 154 months). The children who developed AKI had a median age of 5 months. The most striking observation is th high number of infant admissions to PICU. One hundred and sixteen of the 210 patients (116/210) were infants (age less than 1year) of whom 19/210 were less than 2 months old. Sixteen of the 19 infants less than 2months had AKI. The second finding of note is the high prevalence of AKI in infants (72/116, including those less than 2months old).

There was a male predominance with a male: female ratio of 1.4:1. Most of the patients in the study were from Bloemfontein and Botshabelo (102/210 patients, 48.6%) and (45/210, 21.4%) respectively. Six patients were referred from Ladybrand of whom all 6 had AKI. General paediatrics referred 191 (90.9%) patients while paediatric surgery referred 11 (5.2%) patients and neurosurgery only 8 (3.8%) patients. Pneumonia was the most common primary diagnosis in the entire study population 72/210 (34.3%), as well as in patients who had AKI (33/108, 30.5%). Septic shock was concurrently found in 17/108 (8.0%) of the patients diagnosed with AKI and acute diarrhoeal disease in 18/108 (16.7%) of these patients. Acute kidney injury was only recorded 27/210 (25%). Table 6 gives an outline of the primary diagnoses according to the patient discharge summaries.

Table 6: Breakdown of the primary admission diagnoses for the total study population, patients with AKI and patients without AKI

Primary Diagnosis	Study Cohort n=210 (%)	AKI patients n=108 (%)	Patients without AKI n=102 (%)
Pneumonia	72 (34.3%)	33 (30.5%)	39 (38.2%)
Bronchiolitis	8 (3.8%)	1 (0.9%)	7 (6.8%)
Upper airway obstruction	6 (2.8%)	2 (1.9%)	4 (3.9%)
Status Asthmaticus	1 (0.5%)	0 (0%)	1 (0.9%)
Cardiac failure	4 (1.9%)	4 (3.7)	0 (0%)
Myocarditis	2 (0.9%)	2 (1.9%)	0 (0%)
Traumatic brain injury	9 (4.3%)	1 (0.9%)	8 (7.8%)
Status Epilepsy	4 (1.9%)	0 (0%)	4 (3.9%)
Meningitis	4 (1.9%)	3 (2.7%)	1 (0.9%)
Guillian-Barre syndrome	2 (0.9%)	1 (0.9%)	1 (0.9%)
Acute flaccid paralysis	2 (0.9%)	1 (0.9%)	1 (0.9%)

Other Central Nervous System conditions	4 (1.9%)	0 (0%)	4 (3.9%)
Acute diarrhoea	22 (10.5%)	18 (16.7%)	4 (3,9%)
Hypernatremic dehydration	8 (3.8%)	8 (7.4%)	0 (0%)
Acute liver failure	4 (1.9%)	3 (2.7%)	1 (0.9%)
Chronic diarrhoea	1 (0.5%)	0 (0%)	1 (0.9%)
Bowel obstruction	1 (0.5%)	1 (0.9%)	0 (0%)
Diabetic ketoacidosis	12 (5.7%)	6 (5.6%)	6 (5.8%)
Other endocrine abnormalities	1 (0.5%)	0 (0%)	1 (0.9%)
AKI	1 (0.5%)	1 (0.9%)	0 (0%)
Haemolytic uremic syndrome	2 (0.9%)	2 (1.8%)	0 (0%)
Organophosphate poisoning	5 (2.4%)	3 (2.7%)	2 (1.9%)
Salicylate poisoning	1 (0.5%)	1 (0.9%)	0 (0%)
Hydrocarbon ingestion	1 (0.5%0	0 (0%)	1 (0.9%)
Other poison ingestion	8 (3.8%)	0 (0%)	8 (7.8%)
Sepsis	13 (6.2%)	9 (8.3%)	4 (3.9%)
Other Haematological diagnoses	1 (0.5%)	1 (0.9%)	0 (0%)
Burns	11 (5.2%)	7 (6.4%)	4 (3.9%)

4.3 Characteristics of children with AKI

The median eCCl on admission for patients with AKI was 52ml/min/1.73m^2 and 90.5ml/min/1.73m^2 for the entire study cohort. The lowest eCCl during admission was also recorded with a median of 41ml/min/1.73m^2 in AKI patients. The median lowest eCCl for the studied population was 78 ml/min/1.73m^2. In total 15 patients had an eCCl of <15ml/min/1.73m^2. More than half (61 patients, 56.5%) of patients with AKI had a measured peak serum creatinine and therefore their lowest eCCl on the day of admission. The day of peak measured serum creatinine median was day 1 (minimum day 1 and maximum day 12). After 72 hours approximately 79% of patients had already reached their lowest eCCl as depicted in Table 7.

Table 7: Day of highest recorded creatinine in the study population and patients with AKI

Day of highest serum creatinine	Total study population n=210 (%)	Patients with AKI n=108 (%)
1	138 (65.7%)	61 (56.7%)
2	25 (11.9%)	15 (13.8%)
3	28 (13.3%)	19 (17.5%)
4	4 (1.9%)	3 (2.7%)
5	5 (2.3%)	3 (2.7%)
6	3 (1.4%)	2 (1.8%)
7	1 (0.5%)	1 (0.9%)
>7	6 (2,8%)	4 (3,7%)

A fifth (44 patients, 20.9%) of patients admitted had no urinary catheter during their stay in PICU. Of these 10 (4.8%) patients had AKI. Anuria was only present in 8 (3.81%) cases and oliguria in 31 (14.8%) of patients. More than half (120 patients, 57.1%) of the patients had a normal urine output. Severe metabolic acidosis (defined as a serum pH of less than 7.0) was recorded in 22 (10.5%) patients, with the serum urea raised in 83 (39.5%) children. More than half (115 patients, 54.8%) of patients required inotropic support. Eight (3.8%) patients had multiple organ dysfunction syndrome with AKI present in 7 of these patients. The clinical and laboratory characteristics are shown in table 8.

Table 8: Clinical and laboratory characteristics of the study cohort

Vector	Number of patients n= 210	Percentage of patients %
Severe metabolic acidosis	22	10.5%
No metabolic acidosis	143	68.1%
Elevated serum urea	83	39.5%
Hypernatraemia	35	16.7%
Hyponatraemia	10	4.8%
Hyperkalaemia	11	5.2%
Hypertension	7	3.3%
Sepsis	54	25.7%
Inotropic support	115	54.8%
Multiple organ dysfunction syndrome	8	3.8%

4.4 Outcomes

One hundred and two of the 210 (48.6%) patients admitted to PICU were assisted with mechanical ventilation. Of the patients that were ventilated a third (35 patients, 34,3%) were ventilated for less than 3days and a total of 69 (67,6%) were ventilated for less than 7days (Table 9). The median ventilation days was 0 (lower quartile 0 and upper quartile 69). There were no patients with AKI that needed non-invasive ventilatory support by means of CPAP.

Table 9: Breakdown of respiratory support measures

Number of days supported	Number of patients ventilated n=102	Percentage of ventilated patients %	Number of patients that received CPAP n=48	Percentage of patients that received CPAP %
≤ 3	35	34.3%	33	68.8%
≤ 5	17	16.7%	9	18.8%
≤7	17	16.7%	3	6.2%
≤ 10	17	16.7%	2	4.2%
>10	16	15.6%	1	2.0%

The median length of stay (LOS) for patients with AKI was 5 days (range 1-77days). Twelve patients were admitted for longer than 15 days, 8 of whom had AKI. No patients received haemodialysis and only one patient received peritoneal dialysis. Thirty patients (30/210, 14.2%) demised of whom 20/108 (18.5%) who had AKI died compared to 10/102 (9.8%) who did not have AKI demised.

Chapter 5 Discussion

This study describes AKI in critically ill children admitted to the paediatric intensive care unit of Pelonomi Hospital in Bloemfontein. Over a period of 11 months AKI was diagnosed in 108/210 (51.4%) children admitted to PICU. The most common diagnoses of children admitted with AKI was pneumonia and acute diarrhoeal disease. The mortality rate in children who had AKI was higher compared to children without AKI, (20/108, 18.5%) and (10/102/ 9.8%) respectively.

Although the prevalence of AKI is rising in both developed and developing countries, the recorded prevalence of 51.4% (108 cases in 11months) in this study was higher than expected. In comparison, similar studies (also using the pRIFLE criteria) done in Nigeria and India found a prevalence of 17.4% (35 cases per year) and 40.9% respectively, while the large multicentre AWARE project reported a rate of 26.9%.[8,18,20] A similar rate of 51.0% has been reported in critically ill children admitted to Stanford University associated paediatric intensive care unit.[16] An eCCL of <15ml/min/1.73m^2 was found in 15 patients. The possibility that these patients could already have had chronic kidney disease instead of an AKI episode could not be excluded as this was their first hospital admission.

The majority of patients who are diagnosed with AKI, are diagnosed and maximally categorised as pRIFLE Risk (pRIFLE max).[16,20] One group found that of their 51% of AKI cases, 26.9% were classified as Risk while 18.2% of the cases were categorised as Failure.[16] This trend was also repeated in research from developing counties where 37.9% of AKI patients had a pRIFLE max of Risk in contrast to the 26.2% with a pRIFLE max of Failure.[20] As mentioned in the literature study it is known that stage 1 and stage 3 of the KDIGO criteria is comparable with the Risk and Failure classifications of the pRIFLE criteria.[16,30] Although the AWARE study used the KDIGO definition, the AKI staging could still be compared. According to the AWARE study Stage 1 AKI was present in 13.3% and Stage 3 in 5.3% of the patients with AKI.[8] In this study however, the largest proportion of AKI patients (21.9%) had a pRIFLE max of Failure (or Stage 3). A pRIFLE max of Risk (or stage 1) was only found in 15.2% of patients.

A possible explanation for this shift from the norm lies in the age distribution of the population. The median age of critically ill children included in this study was 8 months, while the median age of AKI cases were 5 months. More than half (116 patients, 55.2%) of the study population was younger than 1 year old with a higher prevalence (72 patients, 62%) of AKI in this age group. In other research done in South Africa, Van Biljon (2008) also found that 65% of AKI cases were less than 1

year old.[21] In the multicentre cohort study the median age was 66 months.[8] The median age of the included cases in the two other studies mentioned above, were 6.5 years and 2.3 years.[16,20] Age as a possible risk factor for AIK can however not be confirmed as this study was unfortunately not powered to do so.

Other possible explanations for the high rate of severe AKI could be the severity of the presenting illness, poor access to health care, late presentation and poor pre-transfer resuscitation. These factors have been documented in research from developing countries. [17-18,21]

The slight male predominance of 1.3:1 (58%) was not unexpected and was demonstrated in multiple other studies.[5,18,21,27] The majority of patients admitted to PICU resided in and around Bloemfontein (102 patients, 48.6%) and 45 (21.4%) patients came from the nearby Botshabelo community. Less than a third of the referrals were from rural areas. Of importance though is the six patients referred from Ladybrand who all had AKI. This might be due to the severity of the presenting illness, but might also demonstrate deficient pre-transfer resuscitation and warrants further investigation. The lack of referrals from rural areas may be due to lack of access to medical care. Most of the admissions were referred from general paediatrics (191 patients, 90.9%) as this was also the discipline with the greatest likelihood for hospital admissions with 74 beds compared to the 30 surgical beds.

Approximately a third (72 patients, 34.3%) of patients admitted to PICU was diagnosed with pneumonia. Septic shock was present in 27 (12.8%) of patients. Although acute diarrhoeal disease was only recorded in 22 (10.5%) of patients, 18 of those patients had AKI. The 0by25 group cited hypotension and dehydration as the most common causes for AKI.[8] Research done in Africa by Esezobor et al (2012) and Antwi et al (2015) attributed primary renal disease as the main aetiological factor, but may be confounded by the fact that the patients in their respective cohorts were from a nephrology unit .[18,34] In another South African study to determine the cause of AKI, haemolytic uremic syndrome and acute tubular necrosis were the most common reason for admission.[21] Other developing countries echoed respiratory and febrile disease as the most common diagnoses on admission.[5,8,20,27] Only 27 (25%) patients had the diagnosis of AKI on their discharge summaries which underscores the fact that AKI was largely under reported. If AKI was not diagnosed, it implies that three quarters of the patients with AKI was missed and lost to follow up.

Most of the patients in the study group (138/210, 65.7%) developed their peak serum creatinine on day 1, while 28/210 (13.3%) reached their peak level by day 3. Other comparable research also found the AKI diagnosis rate on day 1 as high as 90.2%.[17,18,20] This early peak in serum creatinine implies that AKI commonly develop prior to admission in a resource limited setting as demonstrated by the 0by25 group.[22]

In the AWARE study it was found that using only serum creatinine to evaluate for AKI excluded almost two thirds of patients fulfilling the urine output criteria for the diagnosis.[8] This exaggerated

result was not reflected in other research.[17,18,33] Anuria was present in only 8/210 (3.8%) patients and oliguria in 31/210 (14.8%) patients with approximately a fifth (44/210, 20.9%) of patients without accurate urine output monitoring as they had no urinary catheters. Although 120/210 (57,1%) had a normal urine output, AKI may have been missed where the use of the urine output criteria was not possible and this is a major shortcoming of the study. Unfortunately, factors like the use of diuretics were not investigated.

Twenty two of 210 (10.5%) had severe metabolic acidosis. The possible factors contributing to the acidosis were not explored. It remains speculative, but is possible that several factors were simultaneously present in the critically ill patients with shock and septicaemia. Almost 40% (83/210, 39.5%) of children had increased urea levels and 35 (16.7%) were hypernatremic, which is a common finding in dehydrated young infants who are not able to feed.

A quarter (54 patients, 25.7%) of patients admitted to PICU had features of sepsis and more than half (115 patients, 54.8%) required inotropic support. These factors have been well documented to contribute to severity of AKI staging.[3,14,24] Ventilation was needed in 102 (48.6%) patients and approximately two thirds (69 patients, 67.7%) of these patients needed ventilation for less than seven days, but the association of AKI leading to longer ventilation was not studied.

Severe AKI has been associated with a longer length of stay in the PICU.[17,19,20] This was not clearly demonstrated as the median LOS of patients with AKI was 5days while the median LOS in the study population was 4days. Despite the high prevalence of severe AKI and hyperkalemia being present in 11 (5.2%) patients, only 1 (0.9%) patient received renal replacement therapy (RRT). This rate of RRT was much lower than the reported rates of 5.8% to as high as 27.8% in other developing countries.[5,20,27] This might be due to lack of experience with RRT as there is no dedicated paediatric nephrology service at Pelonomi Hospital and patients requiring dialysis are usually transferred to Universitas Hospital.

The mortality rate of 18.5% in patients with acute kidney injury is comparable to the rates found in other research projects. The mortality rate reported by the multicentre AWARE group was only 3.4%, but the majority of patients in this study were from first world countries with better access to care.[8] The 0by25 group published a mortality rate of 12% in lower-middle-income countries.[22] A higher rate of 25.5% was recorded by Van Biljon (2008) in another study in South Africa.[21] The reported mortality rates varied from as little as 3.4% to as high as 46.3% depending on factors like access to medical care, access to renal replacement therapy, poverty and ignorance.[8,18,20-21,27]

The advantage of this study is the comprehensive inclusion of patients throughout the seasonal variation. There are some obvious limitations as well. Firstly, this is an observational retrospective single-centre research project using existing medical records, which were incomplete and lacked important detail required to diagnose AKI. This study was not powered to determine causal relationship between exposures and AKI outcomes. Similar to other research reports from single

centres in a resource constrained environment, the differences of patient populations, inclusion and exclusion criteria, variables investigated, and duration of follow-up after discharge, make comparison impossible. Secondly, in patients where no previous baseline creatinine clearance was known an eCCl of 120ml/min/1,73m^2 was assumed. This may lead to the inclusion of patients with chronic kidney disease as having AKI, but this assumption was based on previous research suggesting a higher eCCl in children.[30,34,37] This may also overestimate the prevalence of AKI in the infant population. Thirdly, no detailed information is available on interventions influencing urine output (e.g. the use of diuretics) which may have had an influence on the diagnostic criteria of AKI and AKI severity. Fourthly, the study was conducted in a tertiary setting and the clinical profile of the patients might be affected by referral bias. Finally, the study was not powered to examine predictors of mortality as this was not the primary outcome.

Chapter 6 Conclusion and recommendations

6.1 Conclusion

This retrospective observational study performed in Pelonomi Tertiary Hospital in Bloemfontein found the prevalence of acute kidney injury in critically ill children to be 51.4% (108 cases in 11months). This highlights AKI as a common occurrence in PICU, with severe AKI being the most prevalent stage. Children younger than 12 months also had a higher risk of developing AKI. The majority of children who developed AKI, did so within the first 72hours. The most common admission diagnosis in PICU were infectious diseases i.e. pneumonia and acute diarrhoeal disease in 72 patients, 34.3% and 22 patients, 10.5% respectively. Acute kidney injury was not recognised in 75% of cases while the patients were in PICU, as demonstrated by the absence of the diagnosis on the discharge summaries. The mortality rate in patients with AKI is higher at 18.5%.

6.2 Recommendations

Future research is needed to not only compare risk factors to outcome in AKI patients, but also the long-term outcomes of AKI, and the subsequent long-term risk of development of chronic kidney disease. Better awareness of the risk of developing AKI in all patients with critical illness will allow early recognition and appropriate management. The diagnosis of AKI has been simplified with the pRIFLE criteria. It can be used at the bedside, allowing promt management before more harm can be done by toxic treatments or before other complications have set in.

Improving morbidity and mortality due to AKI can only be achieved once the condition is identified and quantified. It is trusted that this research project creates awareness regarding the high prevalence of AKI and the importance of making the diagnosis early.

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Appendix A: Data form

Data Form: Acute Kidney Injury in Pelonomi PICU

Study number

1. Age (months)

2. Weight (kg)

3. Length (cm)

4. Gender

   -1 Male

   -2 Female

5. Residing Town

6. Referring discipline

7. Primary diagnosis

8. Secondary diagnosis

9. Length of stay (days) ☐☐☐

10. Admission eCCl (ml/min/1.73m^2) ☐☐☐

11. Admission serum creatinine (mmol/l) ☐☐☐☐

12. Lowest eCCl (ml/min/1.75m^2) ☐☐☐

13. Highest serum creatinine (mmo/l) ☐☐☐☐

14. Day during admission of highest creatinine ☐☐☐

15. Urine output (ml/kg/h) ☐

-1 Anuria: 0ml/kg/h

-2 Oliguria: 0-0.5ml/kg/h

-3 Normal: 0.5 – 5.0 ml/kg/h

-4 Polyuria: >5.0ml/kg/h

-5 No catheter

16. RIFLE stage ☐

-1 Risk

-2 Injury

-3 Failure

-4 Loss

-5 Failure

- 6 Normal renal function

17. Metabolic acidosis

-1 ph <7.0

-2 ph 7.0 – 7.2

-3 ph 7.2 – 7.35

-4 None

18. Increased Urea

-1 Yes

-2 No

19. Hypernatremia (serum sodium >150mmol/l)

-1 Yes

- 2 No

20. Hyponatremia (serum sodium <130mmol/l)

-1 Yes

-2 No

21. Hyperkalemia (serum potassium >6.0mmol/l)

-1 Yes

-2 No

22. Hypertension

-1 Yes

-2 No

23. Sepsis

-1 Yes

-2 No

24. Inotropic support

-1 Yes

-2 No

25. CPAP/BiPAP days

(number of days received)

26. Ventilation days

(number of days received)

27. Multiorgan failure

-1 Yes

-2 No

28. Haemodialysis

-1 Yes

-2 No

29. Peritoneal dialysis

-1 Yes

-2 No

30. Outcome

-1 Discharge

-2 Death

Appendix B: Ethics committee approval letter

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA
UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

IRB nr 00006240
REC Reference nr 230408-011
IORG0005187
FWA00012784

13 November 2017

DR M REYNDERS
DEPT OF PAEDIATRICS AND CHILD HEALTH
FACULTY OF HEALTH SCIENCES
UFS

Dear Dr M Reynders

HSREC 194/2016 (UFS-HSD2016/1510)
PROJECT TITLE: PREVALENCE OF ACUTE KIDNEY INJURY IN THE PAEDIATRIC INTENSIVE CARE UNIT OF PELONOMI HOSPITAL IN BLOEMFONTEIN FOR THE PERIOD OF JANUARY 2015 TO DECEMBER 2015

APPROVED

1. You are hereby kindly informed that the Health Sciences Research Ethics Committee (HSREC) approved this protocol after all conditions were met.
2. The Committee must be informed of any serious adverse event and/or termination of the study.
3. Any amendment, extension or other modifications to the protocol must be submitted to the HSREC for approval.
4. A progress report should be submitted within one year of approval and annually for long term studies.
5. A final report should be submitted at the completion of the study.
6. Kindly use the **HSREC NR** as reference in correspondence to the HSREC Secretariat.
7. 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.

MS MGE MARAIS
HEAD: HEALTH SCIENCES RESEARCH ETHICS COMMITTEE ADMINISTRATION

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