

Risks and recognition of acute kidney injury in children: a local snapshot of an academic hospital complex in central South Africa.

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Abstract

i. Introduction and aim:

Acute kidney injury (AKI) plays a major role in poor patient outcomes and is associated with increased morbidity and mortality. Epidemiological data of children with AKI in low-resource settings are poorly described in the literature. This study aimed to assess the AKI incidence, risks and recognition in hospitalised children in Bloemfontein.

ii. Methods:

We conducted an observational prospective cross-sectional study of all children admitted to the Bloemfontein Academic Hospital Complex on a chosen "index day". All patients aged 1 month to 13 years admitted to the Bloemfontein Academic Hospital Complex on the "index day" were screened for eligibility for entry into the study. We used the Kidney Disease: Improving Global Outcomes (KDIGO) criteria to define acute kidney injury. The identified AKI cases were followed up one week later to determine outcome.

iii. Results:

A total of 128 patients were screened and 58 patients were enrolled on the "index day". The researcher identified acute kidney injury in 14 of the 58 enrolled patients, of which the primary clinical team only identified three. Anaemia ($p=0.005$, OR 7.8, 95% CI 1.5-39.9) was recognised as the most significant inherent risk factor for the development of acute kidney injury. Sepsis ($p=0.003$, OR 7.5, 95% CI 1.7-38.1) and circulatory shock ($p=0.002$, OR 23.9, 95% CI 2.1-1154.7) were the most prominent aetiologies.

iv. Conclusion:

Acute kidney injury is common and largely unrecognised despite risk factors in our setting. We identified aetiological factors common to larger, multi centre studies. Additional strategies are needed to raise awareness of acute kidney injury in central South Africa.

Introduction

- **Background and significance:**

Acute kidney injury (AKI) is characterised by the abrupt onset of renal dysfunction resulting from injurious endogenous or exogenous processes. This leads to a decrease in glomerular filtration rate (GFR) with a rise in serum creatinine and inability to regulate acid and electrolyte balance or excrete wastes and fluid.(1) AKI is a broad clinical syndrome encompassing various aetiologies.

The RIFLE criteria were developed by an international consensus panel and are intended for use in critically ill adults. The RIFLE classifies increasing severity of AKI into five categories (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease). The second definition of AKI was proposed by the Acute Kidney Injury Network (AKIN), which was also based on common markers of kidney function. This definition built onto the RIFLE criteria with a modification to include small changes in serum creatinine. Then in 2012, Kidney Disease: Improving Global Outcomes (KDIGO) completed the first ever, international, multidisciplinary, clinical practice guideline for AKI. The KDIGO Work Group accepted the existing criteria for the diagnosis and staging of AKI and proposed a single definition of AKI that should be useful for practice, research, and public health.

In recent years it has been shown that AKI plays a major role in poor patient outcomes, and several studies have linked the presence of even mild, reversible AKI to prolonged hospital stay, increased morbidity and mortality.(2)(3).

- **Research in context:**

Worldwide epidemiological data on AKI in children are limited. There is a scarcity of information relating to paediatric AKI in Africa, with no data from central South Africa.

Research has shown that the syndrome we experience in low-resource settings is different to that seen in the developed world, therefore, extrapolation of results from studies from the developed countries to children in developing countries may not be valid.(3).

In 2012 an observational cohort was performed at a leading children's hospital in Brazil, where the incidence and association of acute kidney injury (diagnosed by RIFLE criteria) with mortality and length of stay in the intensive care unit was analysed. They found that the incidence of AKI was both significant and directly associated with hospital mortality and the length of stay in the ICU and hospital.(2)

Yi&Zhang published a prospective multi-centre investigation into the aetiology and outcomes of AKI in Chinese children in 2013. They concluded that primary renal diseases are a major risk factor for paediatric AKI; post-renal disease was the leading

cause of paediatric AKI; and sepsis was the leading cause of death. They also came to the conclusion that a better understanding of the aetiology, incidence, and outcomes of paediatric AKI will help in designing effective strategies of early diagnosis and intervention of AKI.(9)

In 2015 the Nigerian Medical Journal published a paper that concluded that the true incidence of AKI, especially in developing countries, remains unknown. Understanding the epidemiology of AKI by using a standard definition helps to find high-risk children – the first step in improving outcomes.(7) Despite efforts to standardise the definition and classification of AKI, there is still inconsistency in application.

The Center for Acute Care Nephrology and the Division of Critical Care at the Cincinnati Children's Hospital Medical Center conducted a multinational, prospective study involving patients admitted to paediatric intensive care units to describe the epidemiological characteristics of children with acute kidney injury. Their findings were published in the New England Journal of Medicine in November 2016. 27% of the patients evaluated had AKI and there was a statistically significant greater risk of death in those cases with AKI. They concluded that acute kidney injury is common and is associated with poor outcomes, including increased mortality, among critically ill children.(6)

The International Society of Nephrology (ISN) has put forth the human rights case statement of Oby25 – i.e. no one should die of untreated acute kidney injury in low-resource regions by 2025. They undertook the Global Snapshot of AKI – a prospective cohort launched globally with many centers participating.(4) The results of this large, multi-center study were published in the Lancet in April 2016 and provides novel, but limited, information about the burden of AKI worldwide, and establishes baseline information to design interventions to raise awareness of AKI, and to develop strategies to improve outcomes. They identified common aetiological factors (hypotension and dehydration) across all countries, which might be amenable to a standardised approach for early recognition and treatment of acute kidney injury, but they unfortunately included a very small number of patients from low-income countries, potentially under-representing the true burden of AKI in these areas.(5)

Glanzmann and Frey published a retrospective case-control study in 2015 where a potential association between drugs and the risk of developing AKI was assessed. Their results suggested that drugs are indeed associated with acute renal dysfunction in critically ill children. Little literature is available on the association between drug therapy and AKI, and the true incidence of drug-induced nephrotoxicity is difficult to determine. Nephrotoxic medication exposure is becoming more prevalent as a primary cause of AKI, comprising approximately 16% of all pediatric inpatient causes of AKI.(10)

- **Added value of this study:**

With this study we aimed to get a better idea of the true incidence of acute kidney injury and its risk factors in our demographic area. No such research exists for central South Africa. The data we collected from our study provides a valuable comparison to both developing and developed nations.

Recognising the syndrome in our own setting and understanding the implication it has on our patient management is vital. The aim of this study was to look at the incidence of AKI among hospitalised children in Bloemfontein, thereby promoting greater awareness of this syndrome among our healthcare staff. Early diagnosis and intervention may help prevent serious morbidity and even mortality in later life.

Aim of the study

- **Primary:**
 - To establish the point incidence of acute kidney injury (AKI) in children admitted to the Bloemfontein Academic Hospital Complex (Universitas, Pelonomi and National Hospitals) on a chosen "index day".
- **Secondary:**
 - To determine the risk factors and aetiologies of AKI in our setting.
 - To determine the diagnosis, management and outcome of AKI in our setting.

Methodology

i. Study design:

This is a prospective cross-sectional observational study. Clinical and laboratory information on all AKI patients were collected on a chosen "index day". Outcome information on the patients were recorded 7 days later.

ii. Study population and sampling:

We screened all children admitted in the Bloemfontein Academic Hospital Complex on the "index day". We aimed for a study participation of 50 to 70 patients.

- **Inclusion:** Patients with confirmed AKI from any aetiology within 3 days of the "index day" were included.
- **Case definition:** A patient had "confirmed AKI" if they met at least one of the KDIGO criteria:
 - a) Increase in Serum Creatinine (SCr) by ≥ 26.5 micromol/L within 48 hours; or
 - b) Increase in SCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
 - c) Urine volume < 0.5 ml/kg/h for 6 hours.
- **Exclusion:** Those excluded from our study were patients younger than 1 month or older than 13 years of age, as well as those with known chronic kidney disease. Patients who did not have a parent or guardian present to sign consent were also excluded, as well as those who did not have a serum creatinine level done within the 72 hours prior to the index day.

iii. Measurement:

Every patient in the study population who had a serum Creatinine level done within the 72 hours prior to the "index day" was entered in the study. Baseline SCr was taken as any result available that was done more than 7 days, but less than 12 months, prior to the result entered into the study. For the acute increase in SCr criterium, we looked at any SCr result that was done less than 48 hours prior to the result entered.

Where no previous data was available, the past renal function was considered normal. The modified Schwartz formula was used to determine an estimated SCr by using the participant's height and a baseline estimated Glomerular Filtration Rate (GFR) of 100ml/min/1.73m² (normal). The likelihood of a child having undiagnosed chronic kidney disease (CKD) is very low (unlike adults), justifying the assumption of a previously normal eGFR.⁽¹¹⁾ Urine output was looked at where available.

According to the latest KDIGO guidelines, there are many types of exposure that may cause AKI. However, the chances of developing AKI after exposure to the same insult depend on a number of susceptibility (inherent) factors. For the participants entered into our study, the exposures and susceptibilities for the acute kidney injury were determined.

Exposure	Susceptibility
Sepsis	Dehydration or volume depletion
Critical Illness	Advanced age
Circulatory shock	Female gender
Burns	Black race
Trauma	Chronic kidney disease
Cardiac surgery (especially with cardiopulmonary bypass)	Chronic diseases (heart, lung, liver)
Major noncardiac surgery	Diabetes mellitus
Nephrotoxic drugs	Cancer
Radiocontrast agents	Anaemia
Poisonous plants and animals (including traditional medication)	

Table 1. Causes of acute kidney injury: exposures and susceptibilities for non-specified acute kidney injury

We have a special interest in the prescribing behaviour of physicians when it comes to the use of nephrotoxic agents, especially since it is being recognised as a common contributing factor to AKI, but little literature is available in paediatrics.(10) For this reason, we included the prevalence of the use of nephrotoxic medications in patients with established AKI, as determined by our definition. For those cases where nephrotoxic medication was prescribed in the presence of AKI, the treating physician was notified in writing on the index day. A printed, generic note was left in the patient's file and the treating physician was also verbally informed (either in person or telephonically).

We then followed up all the identified cases 7 days later to determine how many of them were still being treated with nephrotoxic drugs, but also to determine in how many of them AKI was recognized, and what the clinical team's response was (discontinuation of nephrotoxic drugs/monitoring of urine output and creatinine/consideration of renal replacement therapy). At the follow-up visit the outcome was also determined (mortality/dialysis/renal recovery/planned follow up).

The researcher and study leader collected all the data.

iv. Methodology mistakes / Measurement of errors:

We expected that previous creatinine results would not be available in many patients. By using the modified Schwartz formula (as described above), we allocated a baseline creatinine to each patient where previous results were not available, by looking at the patient's height and a presumed normal estimated glomerular filtration rate (normal renal function). The likelihood of undiagnosed chronic kidney disease in children is very low, but can however not be quantified.

v. **Pilot Study:**

After approval by the Ethics Committee and the Free State Department of Health, a pilot study was conducted among the patients admitted to the Paediatric Intensive Care Unit (ICU) at Universitas Hospital on 20 October 2016 (five patients were entered). The pilot study revealed a few problems that existed with the data capture sheet, and also helped to estimate the amount of time required to complete the consent form and data capture sheet for each patient.

The information received from the pilot study was not included in the data obtained during the rest of the study, and hence not mentioned here, since the study aims to give a snapshot of AKI on a given day.

Analysis of Data

After the data was collected, analysis was conducted by the Department of Biostatistics at the University of the Free State (UFS). Descriptive statistics for continuous and numerical variables were calculated per group. The incidence rate for acute kidney injury was calculated. The associations between acute kidney injury and the exposure and susceptibility factors were calculated using 95% confidence intervals.

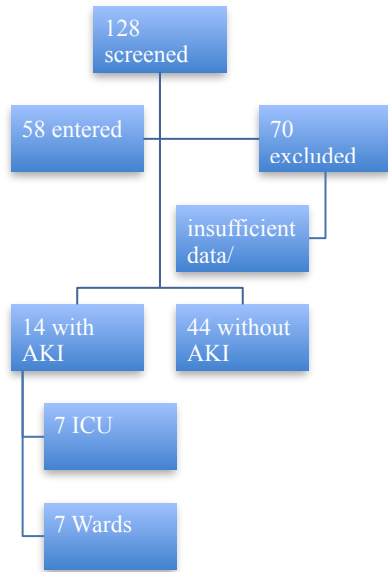
Ethical Considerations

The protocol was submitted to the Health Sciences Research Ethics Committee of the University of the Free State (UFS) for approval in May 2016. According to local regulation, once approval was obtained the Free State Department of Health was contacted for approval, which was obtained in August 2016.

The identities of the participants were kept confidential by using de-identified case report forms. Consent was obtained from each participant's parent or legal guardian. Separate assent was obtained from those children aged 7 to 13 years. If parents gave their approval for research to be carried out with their children, the researcher needed to ascertain whether the child himself had been consulted about his involvement in the research. Children themselves have the right to decide about their participation in research.

It would be unethical to identify the use of nephrotoxic drugs in children with acute kidney injury and then not to intervene to terminate the use of these drugs. For those cases receiving nephrotoxic medication in the presence of AKI, the treating physician was notified in writing on the index day. A printed, generic note was left in the patient's file and the treating physician was also verbally informed in person, or telephonically. The treating physician however had to outweigh the benefit of the use of the drug versus the harm it poses to a child with established AKI, and the ultimate decision to terminate its use lay with him/her.

Results



On 11 October 2016 (the "index day") 128 children were screened, of which 58 patients (46,4%) were entered into the study as cases. 70 patients had either deficient data available, or met one of the exclusion criteria.

Of the 58 patients entered into the study, 14 (24,1%) had acute kidney injury. In the wards, 7 of the 47 (14,9%) patients that were entered into the study had AKI. All ICU patients screened for enrollment were entered, and 7 out of the 11 (63,6%) ICU patients had AKI.

A baseline serum creatinine was assigned to 34 of the 58 study entrants, using the modified Schwartz formula. Of the 14 participants in whom acute kidney injury was diagnosed, the presumed baseline creatinine was used to make the diagnosis in 8.

• **Baseline characteristics**

	Total n=58	AKI n=14
Median age (years)	2.9 (0.1-13.5)	0.7 (0.1-12.3)
Gender		
- Male	34 (58.6%)	7
- Female	24 (41.4%)	7
Ethnicity		
- Black	52 (89.7%)	13
- Coloured	6 (10.3%)	1
- White	0	0

Table 2: Baseline characteristics

The baseline characteristics of study entrants and cases are described in Table 2. The median age of entrants was 2.9 years, versus 0.7 years (about 8 months) for those with AKI. About 60% of entrants were male, but among those with AKI the two sexes were represented equally. Nearly all study entrants were black, which correlates with the demographic served by the participating health care establishments.

• **Risk:**

The results of the exposure and susceptibility risk factors that we screened for are summarised in Table 3. Sepsis (p=0.003, OR 7.5, 95% CI 1.7-38.1) and circulatory shock (p=0.002, OR 23.9, 95% CI 2.1-1154.7) were statistically significant aetiological (exposure) risk factors for acute kidney injury, whereas anaemia (p=0.005, OR 7.8, 95% CI 1.5-39.9) was the most significant inherent (susceptibility) risk factor.

	p-value	Odds Ratio (95% Confidence Interval)	Total Number (Percent of total)	Number with AKI (Percent of those with risk factor)
Exposure				
- Sepsis	0.003	7.5 (1.7-38.1)	21 (36.2%)	10 (47.6%)
- Critical Illness	0.03	4.5 (1.0-19.8)	15 (25.9%)	7 (46.7%)
- Circulatory Shock	0.002	23.9 (2.1-1154.7)	6 (10.3%)	5 (83.3%)
- Burns	1.0	1.05 (0.02-14.4)	4 (6.9%)	1 (25%)
- Cardiac Surgery	1.0	1. (0.0-11.1)	2 (3.5%)	0
- Major noncardiac surgery	1.0	1. (0.0-11.1)	2 (3.5%)	0
- Nephrotoxic drugs	0.13	0.4 (0.1-2.0)	20 (34.5%)	3 (15%)
- Radiocontrast agents	0.6	2.3 (0.2-22.0)	5 (8.6%)	2 (40%)
Susceptibility				
- Dehydration	0.14	3.7 (0.4-31.0)	6 (10.3%)	3 (50%)
- Female gender	0.54	1.6 (0.4-6.3)	24 (41.4%)	7 (29.2%)
- Black race	0.43	2.9 (0.3-137.9)	49 (84.5%)	13 (26.5%)
- Chronic kidney disease	1.0	0.0 (0.0-59.7)	1 (1.7%)	0
- Chronic diseases (heart, lung, liver)	1.0	0.9 (0.1-5.6)	9 (15.5%)	2 (22.2%)
- Cancer	0.08	0.15 (0.0-1.2)	16 (27.6%)	1 (6.3%)
- Anaemia	0.005	7.8 (1.5-39.9)	12 (20.7%)	7 (58.3%)

Table 3: Exposure (aetiological) and Susceptibility (inherent) risk factors for acute kidney injury development

• **Recognition:**

The correct diagnosis of acute kidney injury by the primary physician is visually demonstrated in Chart 1. On the "index day" only 3 of the 14 patients (21,4%) with AKI were correctly diagnosed. At the follow-up visit on 18 October 2016 (7 days

later), after the information sheet was left in the patient’s file, 7 of the 14 (50%) patients had AKI added to their problem list since the previous visit.

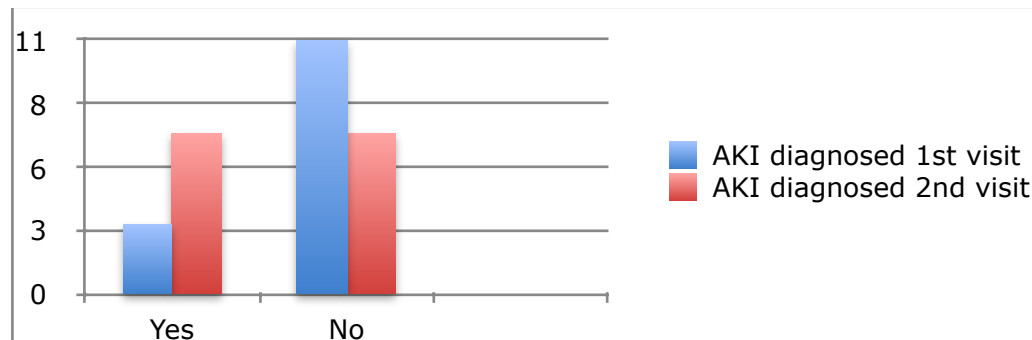


Chart 1: AKI diagnosis by primary physicians

• **Response:**

The clinical team’s response to the diagnosis of acute kidney injury is shown in Table 4. As noted in the methodology of this study, the primary physician was informed of each patient in whom the researcher diagnosed AKI. On the "index day" serum creatinine and/or urine output was monitored in half of the patients with AKI (more than one serum creatinine was done in the 72 hours prior to the index day, or an attempt to monitor the urine output was made), compared to 6 out of the 14 who had a repeat serum creatinine after the index day, but before the follow up day. Of the three patients with AKI, who were on at least one of the listed nephrotoxic drugs, none were discontinued on either the index or follow up visits. At the follow up visit renal replacement therapy was considered in 2 of the patients with AKI.

	Monitor 1 st visit	Monitor 2 nd visit	Consider RRT 1 st visit	Consider RRT 2 nd visit	Discont nephrotoxic drugs 1 st visit	Discont nephrotoxic drugs 2 nd visit
Yes	7	6	0	2	1	3

Table 4: The clinical team’s response to AKI

• **Outcome:**

The outcome at the follow up visit of those patients identified with AKI on the "index day" is shown in Table 5. At the follow up visit 2 of the 14 patients with AKI had already been discharged home. In one of these a follow up creatinine was done, which showed renal recovery, and future follow up was planned, however, in the other patient no follow up creatinine was done and no future follow up was planned. In 9 of the 14 patients there was renal recovery, however in 5 renal recovery was unknown, as no follow up creatinine was tested prior to our second visit. None of the 14 patients required dialysis or died.

	Mortality	Dialysis	Renal Recovery	Planned F/U
Yes	0	0	9	11
No	14	14		1
Unknown			5	2

Table 5: Outcome at follow-up visit

Discussion

Our study is the first local, prospective, cross-sectional study designed to assess the similarities and differences in risk, recognition and outcome of acute kidney injury in central South Africa. We developed this study to compare to the baseline evidence that was provided to the International Society of Nephrology's Oby25 initiative by the Global Snapshot.

We used a modified KDIGO acute kidney injury definition, aiming to capture more children who truly had AKI but without a baseline serum creatinine. By assigning a normal baseline estimated creatinine clearance to those patients in whom no previous laboratory data was available, a baseline creatinine could be calculated by using the modified Schwartz formula. The assumption of baseline normal renal function in children was based on the unlikely chance of previously undiagnosed chronic kidney disease in children.⁽¹¹⁾ The proportion of patients in whom an assigned baseline creatinine was used to make the diagnosis of acute kidney injury is comparable to the assigned proportion out of all the study entrants.

On the "index day", nearly a quarter of study entrants had acute kidney injury, and the diagnosis was correctly made in only 3 of the 14. The comparison of the incidence of acute kidney injury among hospitalised patients in our local snapshot to other international studies remains difficult, as different studies have used different definitions to make the diagnosis. Although our definition for the diagnosis is similar to that used by the ISNs Global Snapshot, they only entered patients with established AKI.

70 of the 128 patients screened during our snapshot could unfortunately not be entered, mostly due to the absence of a recent creatinine result. The hospitals included in this study depend on the National Health Laboratory Service (NHLS) for determination of renal function. Until recently, creatinine was measured routinely in all specimens sent for renal function determination. This is however not the case anymore, and creatinine has to be specifically ticked on the request form. As a result, many patients in whom blood specimens are sent for renal function determination have no creatinine result. The true prevalence in our setting remains therefore largely unknown, but is expected to be in the region of 25%. Previously reported rates of acute kidney injury among children vary widely – from 5% to 82%.⁽⁶⁾ The prevalence of AKI among patients admitted to ICU remains high (63%), which is comparable to other studies.

- **Baseline characteristics:**

The KDIGO guidelines highlight female gender and black race as inherent risk factors for acute kidney injury. Our research is comparable with regards to gender and showed that 29% of the females had AKI, versus 20% of the males. The demographic

profile of the patients seen during our local snapshot makes it impossible for us to quantify black race as a risk factor.

The median age of cases with acute kidney injury in our local snapshot was much lower than that of the entrants, as well as that found in the Global Snapshot and other studies referenced.

- **Risk:**

Sepsis and circulatory shock were the most significant aetiological risk factors for acute kidney injury in our study population. Dehydration (contributing to hypotension and shock), infections and sepsis were the most common aetiological factors in all countries (low-, middle-, and high-income) and all age groups surveyed by the Global Snapshot. Their reported data for the younger populations in low-income countries revealed the same findings, with dehydration and infections being the main drivers of acute kidney injury.

We screened patients for multiple inherent risk factors for the development of AKI, with anaemia being the most statistically significant in our study. The epidemiology of acute kidney injury described in the New England Journal of Medicine in November 2016 revealed that underlying haematological disorders had the highest odds ratio for the development of AKI.(6) Anaemia was the third most prevalent comorbidity in all ages in the Global Snapshot, falling behind obesity and diabetes mellitus. None of our enrolled cases suffered from either obesity or diabetes. Consequently, the most important exposure and susceptibility risk factors in our local snapshot is comparable to that of large, multi-center studies.

- **Recognition and response:**

The secondary aim of this local snapshot was to determine the diagnosis and management of acute kidney injury in our setting. As postulated, acute kidney is largely underdiagnosed. At the follow up visit we looked at the clinical team's response to the diagnosed acute kidney injury, with either monitoring of creatinine and/or urine output, consideration of renal replacement therapy, and discontinuation of nephrotoxic drugs.

- **Outcome:**

We also looked at the outcome of our cases at the follow up visit. Due to the nature of this study, few deductions can be made from our results. However, it is concerning that there were patients in whom long-term follow up was not planned. Children who survive acute kidney injury are at risk for chronic kidney disease, hence long-term follow up of these survivors is warranted.(6) The Global Snapshot confirmed that less than 50% of acute kidney injury survivors (adults and children) had renal follow-up arranged at discharge. Appropriate management of patients with incomplete kidney recovery might delay the progressive loss of kidney function.(5) Educational

campaigns, for all health-care personnel, on the importance of long-term follow-up of patients with AKI need to be developed and implemented.

Conclusion and Recommendations

Our local snapshot is a unique observational prospective cross-sectional study designed to capture the incidence, risk, recognition and outcome of acute kidney injury in children in central South Africa. The study provides novel, although limited, information about the burden of acute kidney injury in our setting. This attempt to establish baseline information can be used to design interventions to raise awareness of acute kidney injury, and to develop strategies to improve outcomes.

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Participants

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A. Appendices

1. Health Sciences Research Ethics Committee letter of approval
2. Free State Department of Health letter of approval
3. Data capture sheet
4. Raw data
5. Participant information document (English, Afrikaans, and Sotho)
6. Consent form (English, Afrikaans, and Sotho)
7. Child assent form (English, Afrikaans, and Sotho)
8. Information document to treating physician