

**An audit of acute kidney injury: a prospective study of the epidemiology,
management and outcome of patients with acute kidney injury, over a 12 month
period at Groote Schuur Hospital, Cape Town, South Africa.**

by

THANDIWE ANGELA LERATO DLAMINI

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Supervisor: Professor Brian Rayner

Division of Nephrology and Hypertension, Department of Medicine

University of Cape Town

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ABSTRACT

An audit of acute kidney injury - a prospective study of the epidemiology, management and outcome of patients with acute kidney injury, over a 12 month period at Groote Schuur Hospital, Cape Town, South Africa (a tertiary level teaching hospital).

Introduction:

Acute kidney injury results from a rapid decline in kidney function. There are many potential causes, some of which are preventable. It carries the risks of mortality, progression to chronic kidney disease and worsening of pre-existing chronic kidney disease. There is a scarcity of data on the epidemiology of acute kidney injury in sub-Saharan Africa. The aims of this study were to describe the epidemiology of acute kidney injury at Groote Schuur hospital, and factors associated with mortality and renal recovery.

Methods:

This was a prospective observational study of patients with acute kidney injury, referred to Groote Schuur Hospital Renal Unit from the 8th of July 2012 to the 8th of July 2013. Ethics approval was granted by the University of Cape Town Human Research Ethics Committee. We excluded patients younger than 13 years, kidney transplant patients, and those not fulfilling the consensus definition of acute kidney injury according to the Kidney Disease: Improving Global Outcomes (KDIGO) group. Data on patient demographics, medical history, clinical observations, investigations, and cause of acute kidney injury was collected from a clerking sheet designed for the study. Patients were followed up at, or after 3 months (90 days) for assessment of survival and renal recovery. The main outcomes were recovery of renal function and mortality at 3 months. Data was entered into an Excel spreadsheet, and imported onto Stata 12.1 for analysis.

Results:

A total of 366 patients were included. The median age was 44 years (IQR 14-82). Of these 214 were male (58.5%). Referrals were from medical, surgical and obstetrics and gynaecology departments. The majority, 217 (59.3%) were medical referrals. Most, 265 (72.4%) had community acquired acute kidney injury. The majority of the 101 patients with hospital acquired acute kidney injury, 72 (71.3%) had severe, stage 3 acute kidney injury. Hypertension was the commonest co-morbidity, present in 152 (41.5%) of the patients. There were 75 (20.6%) HIV positive patients. Acute tubular necrosis was the most common cause of acute kidney injury, identified in 251 (68.6%) patients. Renal biopsies were carried out in 36 (9.8%) patients. More than half, 202 (55.2%), of the patients were in the intensive care unit, while 204 (55.7%) were dialysed. Fluid input was recorded in 140 patients (38.3%). Overall 3 month mortality was 38.8% (142 patients). Of the 224 surviving patients, 119 (53.1%) had a follow up serum creatinine. Of these, 95 (80.5%) had full renal recovery, and 4 (3.4%) went on to end stage renal disease. On multivariate analysis, mechanical ventilation was strongly associated with mortality at 3 months (OR 2.46, p-value 0.019, 95% CI 1.41-4.03). Sepsis had a borderline significant association with 3 month mortality (OR 1.83, P-value 0.066, 95%CI 1.02 – 3.27), as did prolonged time to dialysis (OR 1.93, p-value 0.080, 95% CI 0.93 – 4.03). HIV was not associated with mortality on univariate analysis (OR 1.07, p-value 0.801, 95%CI 0.64-1.80).

Conclusions:

Acute kidney injury carries a high mortality risk, most significant in mechanically ventilated patients. Sepsis and, in those dialysed, late dialysis, may be associated with a high risk of mortality. Efforts to reduce hospital acquired acute kidney injury and to improve patient fluid balance chart records should be made.

TABLE OF CONTENTS

List of Tables.....	5
List of Appendices.....	6
LITERATURE REVIEW.....	8
Literature search strategy.....	8
Definition and background of acute kidney injury.....	8
Epidemiology of acute kidney injury:.....	15
Prevention and management of acute kidney injury:.....	22
Outcomes of acute kidney injury:.....	29
Identification of gaps and needs for further research.....	31
Aims and Objectives.....	33
Methods.....	33
<i>Study Design</i>	33
<i>Setting</i>	33
Eligibility Criteria.....	34
<i>Inclusion criteria</i>	34
Exclusion criteria.....	35
Study Procedures.....	35
Data Collection and management.....	36
<i>Data collection instrument</i>	36
<i>Demographic and Epidemiological data</i>	36
<i>Management data</i>	37
<i>Dialysis data</i>	37
<i>Outcome data</i>	37
Data management and validation.....	38
Statistical Considerations.....	38
<i>Categorical data</i>	38
<i>Continuous data</i>	39
<i>Analysis of potential associations with mortality</i>	39
Ethical Considerations.....	40
RESULTS.....	40

EPIDEMIOLOGY	40
<i>Demographics</i>	40
<i>Risk factors</i>	43
<i>Associations and causes of acute kidney injury</i>	44
PREVENTION AND MANAGEMENT	49
<i>Timing of dialysis</i>	51
OUTCOMES	52
<i>Mortality</i>	52
<i>Renal recovery</i>	57
DISCUSSION	61
Epidemiology	61
Outcome	67
Study limitations	72
REFERENCES	76

List of Tables

Table 1	42-43
Table 2	44-45
Table 3	47-48
Table 4	49-50
Table 5	51
Table 6	54
Table 7	55-56
Table 8	56
Table 9	57
Table 10	59
Table 11	59
Table 12	60

List of Appendices

Appendix 1 (Ethics approval)	95
Appendix 2 (Data capture instrument and clerking sheet).....	96-97
Appendix 3 (Renal biopsy results).....	98-99
Appendix 4 (Groote Schuur Hospital Statistics year 2011/2012).....	100

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LITERATURE REVIEW

Literature search strategy

Literature review involved searching for studies and reports on acute kidney injury using Medline, pub med, and Google Scholar. Key search words included acute kidney injury epidemiology, management and outcome. In addition, the terms acute kidney injury in developing countries, developed countries, Africa and South Africa were also used. Articles using the consensus definition of acute kidney injury were given preference. This is due to the fact that there was no clear biochemical definition of the condition prior to this, resulting in epidemiological data that was not reliable. However, landmark studies preceding the consensus definition of acute kidney injury were also reviewed.

Definition and background of acute kidney injury

Background

Acute Kidney Injury is a syndrome that is characterized by an acute decline in kidney function (Bellomo, Kellum et al. 2012). There are numerous possible causes, ranging from volume responsive conditions to intrinsic renal parenchymal injury, urological obstruction and vascular occlusion (KDIGO 2012).

The term acute kidney injury (AKI) was coined by the Acute Dialysis Quality Initiative (ADQI) group in 2004, together with the RIFLE criteria (Bellomo, Ronco et al. 2004).

This was in an effort to address the lack of an agreed definition of the syndrome, which

was previously termed acute renal failure and which had over 35 definitions assigned to it (Kellum, Levin et al. 2002). The previous lack of a clear definition of acute kidney injury hampered efforts to investigate the epidemiology and full clinical and socioeconomic impact of this condition (Kellum, Levin et al. 2002).

RIFLE classification

The ADQI group defined and classified acute kidney injury according to the RIFLE criteria (Bellomo, Ronco et al. 2004). RIFLE is an acronym that describes increasing severity classes of renal impairment and outcome (Bellomo, Ronco et al. 2004). The severity classes of renal impairment are classified as Risk, Injury and Failure and are based on the most abnormal result amongst serum creatinine, glomerular filtration rate (GFR) and urine output. In addition, outcome criteria are described by the terms Loss and End stage renal disease, and are based on the duration of the kidney injury. In this way, RIFLE encompasses the full spectrum of acute kidney injury, from impairment of renal function to development of chronic kidney disease (KDIGO 2012).

According to the RIFLE criteria, acute kidney injury can be diagnosed in the presence of a fall in GFR of >25% or an increase in serum creatinine of 1.5 times from baseline over a 1-7 day period. It can also be diagnosed by a fall in urine output of <0.5ml/kg/hour in 6 hours (Bellomo, Ronco et al. 2004). This diagnostic criterion incorporates the Risk severity class. Injury is defined as either a 50% fall in GFR, a doubling of serum creatinine or a fall in urine output of <0.5ml/kg/hour for 12 hours. Failure is determined by changes in the level of serum creatinine whether in the form of an increase in serum creatinine of >75% from baseline, an increase of more than three times from baseline, or a level greater than 354µmol/l provided there was an increase of >44.4µmol/l from

baseline. In addition, Failure is diagnosed if a patient has a fall in urine output of $<0.3\text{ml/kg/hr}$ for 24 hours, or anuria for 12 hours. Loss is described as irreversible or persistent acute kidney injury for more than 4 weeks, and End stage renal disease if this persists for more than 3 months (Bellomo, Ronco et al. 2004).

AKIN classification

In 2007 the Acute Kidney Injury Network (AKIN) group modified the RIFLE classification of acute kidney injury by adding the rise in serum creatinine of $26.4\mu\text{mol/l}$ within 48 hours, because this had been shown to carry a mortality risk in various studies. In addition acute kidney injury could be diagnosed if there was a fall in urine output of $<0.5\text{ml/kg/hour}$ in > 6 hours, as defined by the RIFLE criteria (Mehta, Kellum et al. 2007).

The AKIN definition specified that patients first be fully resuscitated if determined to be volume responsive and that urinary tract obstruction be excluded. In addition, a new severity staging system was added. Stage 1 incorporated the serum creatinine increase of $\geq 26.4\mu\text{mol/l}$ from baseline, or a serum creatinine increase of a multiple of 1.5-2 from baseline, as well as the urine output requirements for the definition of acute kidney injury. Stage 2 combined the Injury and Failure criteria of RIFLE and stage 3 was similar to the Failure stage of the RIFLE criteria, but with the addition of an increase in serum creatinine of $26.4\mu\text{mol/l}$ above $354\mu\text{mol}$, to incorporate the rise associated with increased risk of mortality (Mehta, Kellum et al. 2007).

KDIGO classification

The ability of both the RIFLE and AKIN criteria to predict mortality and severity of patient illness has been validated by numerous studies. However, studies have also shown that reliance on only one of these criteria to the exclusion of the other may miss some cases of acute kidney injury (KDIGO 2012). The Kidney Disease: Improving Global Outcomes (KDIGO) group has therefore combined both the AKIN and ADQI definitions in an attempt to provide a unified consensus definition of acute kidney injury (KDIGO 2012). This unified definition is also intended to enable uniformity for public health, clinical practice and research purposes (Lopes, Jorge 2013).

The KDIGO definition incorporates the AKIN requirement of an increase in serum creatinine of $\geq 26.5\mu\text{mol/l}$ within 48 hours (The AKIN group had specified $26.4\mu\text{mol/l}$ which is the equivalent of 0.3mg/dl as opposed to the slightly different $26.5\mu\text{mol/l}$ that is used in the KDIGO classification). The KDIGO definition also incorporates the ADQI RIFLE criteria in the requirement for an increase in serum creatinine by a multiple of 1.5 from baseline, over 7 days. Additionally, a decrease in urine output by $< 0.5\text{ml/kg/hour}$ for > 6 hours also fulfils the requirements for the diagnosis of acute kidney injury (KDIGO 2012).

The KDIGO group stages acute kidney injury for severity according to the AKIN criteria, using the more severe criterion between urine output and serum creatinine deterioration (Lopes, Jorge 2013, KDIGO 2012). According to this staging system, patients in whom renal replacement therapy is initiated are classified under stage 3 acute kidney injury (KDIGO 2012).

Significance of acute kidney injury

Acute kidney injury can lead to the development of chronic kidney disease. In patients with pre-existing chronic kidney disease, it accelerates progression to end stage renal disease and carries a mortality risk (Chertow, Burdick et al. 2005, Go, Chertow et al. 2004, Lafrance, Miller 2010).

In clinical practice there may be opportunities to identify patients at risk of developing acute kidney injury and to institute preventive measures (KDIGO 2012). Such measures may include pre-hydration before administering intravascular iodine based radio-contrast agents to reduce the risk of contrast induced acute kidney injury (Anathhanam, Lewington 2013, Abelha, Botelho et al. 2009, KDIGO 2012). The early recognition of the underlying cause of acute kidney injury provides the opportunity to reverse or halt progression, such as the relief of urological obstruction or administration of immunosuppressive therapy for crescentic glomerulonephritis (KDIGO 2012).

Problematic areas

Serum creatinine

Although the consensus definition of acute kidney injury is an important advancement, it is based on imperfect biomarkers for acute kidney injury (KDIGO 2012, Waikar, Liu et al. 2008). Serum creatinine levels can be increased by drugs such as trimethoprim without a decrease in GFR, by inhibition of renal tubular secretion of creatinine (Berglund, Killander et al. 1975, Andreev, Koopman et al. 1999). Serum creatinine

levels are also influenced by a patient's muscle mass, because creatinine is the product of muscle metabolism (Lopes, Jorge 2013, Andreev, Koopman et al. 1999). Another drawback with serum creatinine as a biomarker for acute kidney injury is that its increase lags behind the fall in glomerular filtration rate, which can delay diagnosis, resulting in late initiation of treatment (Bonventre 2007).

Urine output

Although a fall in urine output may be a physiological response to hypovolemia, its use as a marker of acute kidney injury remains important (Macedo, Malhotra et al. 2011, Kellum 2008). In a study by Macedo et al to assess the efficacy of urine output criteria in detecting acute kidney injury in intensive care unit (ICU) patients, additional episodes were diagnosed using urine output, as opposed to using serum creatinine alone (Macedo, Malhotra et al. 2011). However, the use of urine output as a marker of acute kidney injury also has potential drawbacks, for example, acute kidney injury may be non-oliguric if due to conditions such as aminoglycoside toxicity (KDIGO 2012).

In response to the problems with the use of urine and serum creatinine in defining and detecting acute kidney injury, studies have looked at the use of novel urine and serum injury or damage biomarkers, the increase in which precedes changes in serum creatinine and urine output (Vanmassenhove, Vanholder et al. 2013). These include neutrophil gelatinase associated lipocalin (NGAL), interleukin 18 (IL-18), kidney injury molecule 1 (KIM1), and liver-type fatty acid binding protein (L-FABP) (Siew, Ware et al. 2011, McCullough, Shaw et al. 2013). The proposed benefit of these biomarkers is the

potential for early detection of acute kidney injury, thus enabling prompt action to reverse or prevent further decline in renal function (Vaidya, Ferguson et al. 2008).

However, the use of the novel biomarkers is not without its limitations. An example of one such limitation was seen in a study which found that variations in NGAL levels have better predictive ability for acute kidney injury in paediatric cases rather than in adult cases (Haase, Bellomo et al. 2009).

Levels of NGAL may also be affected by systemic and urinary tract infections, while levels of IL-18 may remain unchanged in pre-renal acute kidney injury, thus limiting their diagnostic utility (Parikh, Devarajan 2008). NGAL has also been found to have varying sensitivities and specificities depending on the stage of acute kidney injury. If a patient has mild acute kidney injury, NGAL is less useful as a diagnostic biomarker. However, as the severity of acute kidney injury increases, NGAL levels rise, making it a more reliable biomarker at this stage (Waikar, Betensky et al. 2012, Haase, Bellomo et al. 2009). A further study in adult cardiac surgery patients found NGAL to have better predictive ability for acute kidney injury among patients with normal pre-operative baseline serum creatinine, compared to those who started off with an abnormal baseline (McIlroy, Wagener et al. 2010). Ultimately, the biggest drawback to the use of these novel biomarkers in clinical practice at the moment is their prohibitive cost (KDIGO 2012) which means that their effectiveness cannot be tested in developing countries.

Epidemiology of acute kidney injury:

Early studies of acute kidney injury provided important epidemiological data that identified risk factors such as patient age, co-morbidities, intensive care unit (ICU) acquired acute kidney injury, the use of renal replacement therapy (haemodialysis), major surgery and the use of intravascular iodine based radio-contrast. (Shusterman, Strom et al. 1987, Liano, Pascual 1996, Nash, Hafeez et al. 2002). These early studies also showed that a small rise in serum creatinine was associated with mortality.

However, while these studies were helpful in identifying patients at risk, there was often a wide variation in reported epidemiological data in similar regions, contributed to by the varied definitions of acute kidney injury that were employed. This affected the ability to appreciate the full impact of acute kidney injury.

The consensus definition of acute kidney injury has provided a standardized tool for researching acute kidney injury and has made it possible to provide more reliable data on incidence and outcome (KDIGO 2012). This can help identify a true pattern of acute kidney injury in a geographical region which can aid with the implementation of preventive strategies, such as the allocation of medical and human resources (Cerdeira, Lameire et al. 2008, Lameire, Bagga et al. 2013) .

Incidence and mortality

Recent reports from developed countries such as the United States of America and Australia suggest that the incidence of acute kidney injury is rising, whilst the overall mortality rate is falling (Hsu, McCulloch et al. 2007, Waikar, Liu et al. 2008, Bagshaw,

George et al. 2007). In a retrospective analysis of ICU patients with acute kidney injury over a ten year period, Bagshaw et al found that although mortality rates were still high, the overall trend showed a decline over this period (Bagshaw, George et al. 2007). It is difficult to extrapolate these findings to Africa, as there is a paucity of epidemiological studies from the region (Naicker, Aboud et al. 2008).

In addition, a review of current data reveals that the incidence of acute kidney injury can also vary depending on the population studied and the definition used for determining acute kidney injury. An example of variations in population studies is seen in incidence reports that range from 5000 cases per million per year in patients that do not require dialysis, to a lower rate of 295 cases per million per year for patients requiring dialysis (Bellomo, Kellum et al. 2012).

Regional differences

Studies suggest that there are differences in the epidemiology of acute kidney injury, depending on whether a region is classified as developed or developing (Cerdá, Bagga et al. 2008). These differences may be with respect to patient age, risk factors, cause and whether acute kidney injury is acquired in the community or in the hospital.

Data from developed countries shows acute kidney injury to be most common in older patients. These patients typically have multiple co-morbidities (such as heart failure) and are managed in an ICU setting (Cerde, Lameire et al. 2008). Hospital acquired acute kidney injury is therefore more common in this context (Cerdá, Bagga et al. 2008).

In developing countries, the epidemiology of acute kidney injury differs depending on whether one is in an urban or non-urban setting. In non-urban areas, acute kidney injury

affects younger patients. Patients tend to present with a single cause of acute kidney injury, including communicable diseases (such as malaria and infective gastroenteritis), obstetric causes (such as septic abortions and pre-eclampsia) and nephrotoxins (Naicker, Aboud et al. 2008, Okunola, Ayodele et al. 2012, Kaballo, Khogali et al. 2007, Cerdá, Bagga et al. 2008). Community acquired acute kidney injury is common in this context (Cerdá, Bagga et al. 2008). In contrast, the epidemiology of acute kidney injury in urbanized areas of developing countries is similar to that found in developed countries in that it is likely to present itself in older patients with co-morbidities and to be classified as hospital acquired (Lombardi, Yu et al. 2008).

Causes

Acute kidney injury can arise from pre-renal causes such as diarrhoeal illnesses, intrinsic renal causes (such as acute tubular necrosis, acute interstitial nephritis and glomerulonephritis), obstruction, and vascular causes. The detection of the underlying cause of acute kidney injury is important as some causes require prompt specific therapy, such as the relief of urological obstruction (KDIGO 2012). Acute kidney injury can also be precipitated by the prevailing risk factors present in different communities (Okusa, Chertow et al. 2009). For instance, patients from tropical areas may present with infectious diseases such as malaria and risks associated with envenomation by poisonous snakes (Cerde, Lameire et al. 2008, Cerdá, Bagga et al. 2008).

Literature also points towards some unique epidemiological features due to infection with the human immunodeficiency virus (HIV), which is an important co-morbidity in many South Africans (Fabian, Naicker 2009, Wyatt, Arons et al. 2006, Arendse,

Okpechi et al. 2011, Lopes, Melo et al. 2011, Shisana, Rehle et al. 2009). Mortality rates were reported to be around six times higher among hospitalized HIV positive patients in the pre-highly active anti-retroviral therapy (HAART) era (Wyatt, Arons et al. 2006, Naicker, Aboud et al. 2008). Since the widespread use of HAART, the trend in outcome of HIV positive patients with acute kidney injury has largely been similar to that of HIV negative patients (Nel, Moosa et al. 2012). In Cape Town, Arendse et al demonstrated a better outcome for HIV positive patients with CD4 counts greater than 200, compared to those with lower CD4 levels (Arendse, Okpechi et al. 2011).

Pathological causes of acute kidney injury

Acute tubular necrosis is the most common cause of acute kidney injury (Waikar, Liu et al. 2008). The term itself is problematic as it is derived from studies of animal models where cortical necrosis arose from severe hypo-perfusion (Bellomo, Kellum et al. 2012, Devarajan 2005, Dunnill 1974). This is not typically the case in humans, where the pathological findings tend to be milder and to be due to tubular cell apoptosis rather than necrosis (Devarajan 2005). In humans, cortical necrosis is only found in cases of significant renal hypo-perfusion such as severe post-partum haemorrhage (Dunnill 1974).

While the definitive diagnosis of acute tubular necrosis is based on histology, in clinical practice this tends to be according to the clinical setting, urine microscopy (such as the finding of muddy brown granular casts and tubular epithelial cells) and the course

(Esson, Schrier 2002). Causes of acute tubular necrosis include sepsis, nephrotoxins, and hypo-perfusion (Dunnill 1974).

Sepsis

Sepsis is a common cause of acute tubular necrosis where tubular injury results from inflammatory cytokine mediated intra-renal vasoconstriction and tubular apoptosis (Zarjou, Agarwal 2011). A study conducted in the North of Scotland found sepsis to be a leading cause of acute kidney injury in that region in that it was found in 47% of the patients (Ali, Khan et al. 2007).

Nephrotoxins

Acute kidney injury induced by nephrotoxins often presents differently depending on the regional context (Naicker, Aboud et al. 2008). For instance studies from South Africa highlight the use of herbal remedies as an important cause of nephrotoxicity (Luyckx, Steenkamp et al. 2005). The types of remedies used vary from herbal treatment of infertility to medicinal use for acute or chronic illnesses. This can be difficult to detect as some patients may not volunteer information about the use of such remedies (Luyckx, Naicker 2008, Swanepoel, Blockman et al. 2008). However, their detection as a cause of acute kidney injury provides an opportunity to educate against their future use in patients who survive (Swanepoel, Blockman et al. 2008). Although acute tubular necrosis is a common histopathological finding from these nephrotoxins, other acute renal histopathological patterns include acute interstitial nephritis and glomerular injury (Luyckx, Naicker 2008).

Other nephrotoxins are synthetic or 'over the counter' preparations, such as potassium dichromate. Potassium dichromate is a component of some laxatives used by sections

of the South African population who believe them to be a 'detoxification' agent (Swanepoel, Blockman et al. 2008).

Studies in developed countries have identified intravascular iodinated radio-contrast media as an important potential nephrotoxin, causing contrast induced nephropathy (Hoste, Doom et al. 2011, Nash, Hafeez et al. 2002, Waikar, Liu et al. 2008). There are three principal mechanisms involved in contrast induced nephropathy. The first mechanism is through direct renal tubular toxicity by the iodinated radio-contrast agent, which causes disruption of mitochondrial function, creation of free radicals, and induction of renal tubular apoptosis. The second mechanism is through the induction of vasoconstriction by the radio-contrast agent, which reduces blood flow through the relatively hypoxic renal medulla, causing ischaemia and tubular cell damage. Thirdly as another consequence of ischaemia, there is resultant formation of reactive oxygen species in the medulla, and these reactive oxygen species react with nitrogen to form peroxynitrite, which is itself toxic to the renal tubules (Markota, Markota et al. 2013).

In the large epidemiological study of hospital acquired acute kidney injury by Nash et al, that preceded the consensus definition of acute kidney injury, contrast induced nephropathy was the third leading cause of hospital acquired acute kidney injury, accounting for 11% of cases (Nash, Hafeez et al. 2002). Risks of developing contrast induced nephropathy are increased with the use of high volume doses and those with high osmolality (McCullough 2008). Other pharmacological agents with nephrotoxic potential include aminoglycosides and amphotericin B, which typically cause non-oliguric acute kidney injury (KDIGO 2012).

Acute kidney injury in surgical and Obstetrics and gynaecology cases

Amongst surgical patients, risk factors for acute kidney injury include advanced age, high risk surgery, the presence of co-morbidities, and intra-operative use of inotropes (Kheterpal, Tremper et al. 2007). Furthermore acute kidney injury may result from abdominal compartment syndrome following abdominal surgery (Raeburn, Moore et al. 2001, Maerz, Kaplan 2008). The resultant rise in intra-thoracic pressure following surgery is one of the mechanisms by which acute kidney injury may arise (Maerz, Kaplan 2008). Increased intra-thoracic pressure reduces venous return, which in turn increases renal vein pressures. It also causes increased extrinsic retroperitoneal pressure resulting in reduced glomerular filtration (Maerz, Kaplan 2008).

In major vascular surgery, acute kidney injury can result from athero-emboli if there was pre-existing atherosclerosis. Other causes include the duration of supra-renal aortic clamp time and the inflammatory response resulting from the surgical procedure (Welten, Chonchol et al. 2008).

In cardiac surgery acute kidney injury can arise from renal hypo-perfusion and a fall in mean arterial pressure, leading to ischaemia (Karkouti, Wijeyesundera et al. 2009). Other postulated causes include cytokine mediated effects induced firstly by the surgical procedure and secondly by the contact of blood with the cardiopulmonary bypass circuit. A further possible reason is nephrotoxicity caused by the release of free haemoglobin and iron into the circulation during the procedure (Karkouti, Wijeyesundera et al. 2009).

Amongst obstetrics and gynaecology patients, causes of acute kidney injury reported in developing countries include acute tubular necrosis as a result of peri-partum haemorrhage (Okunola, Ayodele et al. 2012). For instance, in parts of Nigeria acute kidney injury in obstetrics and gynaecology patients has been linked to poor antenatal care, highlighting the important potential role of prevention (Okunola, Ayodele et al. 2012, Naicker, Aboud et al. 2008). Pre-eclampsia is another important cause of acute kidney injury, and is mainly caused by soluble vascular endothelial growth factor that causes glomerular endothelial swelling and loss of fenestrae (Stillman, Karumanchi 2007, Naicker, Aboud et al. 2008) .

Prevention and management of acute kidney injury:

As there is currently no specific treatment for acute tubular necrosis, which is the most common cause of acute kidney, prevention remains essential in its management (Chawla, Amdur et al. 2011). For other causes of acute kidney injury such as crescentic glomerulonephritis, or urological obstruction, a basic approach including urinalysis and kidney ureter ultrasonography can identify patients that can benefit from directed therapy such as immunosuppression and relief of the obstruction respectively (KDIGO 2012).

Preventive strategies

There are many steps that clinicians can take in the management of patients to prevent, reverse or halt acute kidney injury (KDIGO 2012, Venkataraman 2008). For critically ill patients, the principles of early goal directed therapy can be employed (Rivers, Nguyen

et al. 2001, KDIGO 2012). Rivers et al conducted a single centre randomized controlled study comparing early goal directed therapy to standard therapy (Rivers, Nguyen et al. 2001). Early goal directed therapy involved assigning patients with severe sepsis to prompt management, to achieve pre-determined clinical parameters within six hours of their admission to ICU. Although acute kidney injury was not an outcome measure in this study, the patients with early goal directed therapy had better urine output and lower in-hospital mortality (Rivers, Nguyen et al. 2001).

A preventive strategy that is in use in hospitals in the United Kingdom involves the use of an 'early warning score', a scoring system that is incorporated into the patient's observation charts. This system has been shown to correlate to mortality and to aid early detection of deteriorating patients, thus enabling prompt intervention (Goldhill, McNarry et al. 2005).

Patients requiring intravascular iodine based radio-contrast in diagnostic procedures have been shown to have reduced risks of contrast induced acute kidney injury if intravascular pre-hydration is instituted (Venkataraman 2008). One study showed additional benefit from both intravenous pre-hydration and alkalinisation of urine to a pH of greater than 6, with oral citrate. This effect was attributed to a resultant reduction in the formation of nephrotoxic free-radicals (Markota, Markota et al. 2013).

Fluid therapy is vital for patients with volume responsive acute kidney injury (KDIGO 2012). However, caution should be taken to avoid fluid overload as studies have clearly linked fluid overload to an increased risk of mortality (Vincent, Sakr et al. 2006, Payen, de Pont et al. 2008, Teixeira, Garzotto et al. 2013).

Many studies have looked at the effects of specific types of colloids and crystalloids on renal injury and patient mortality (KDIGO 2012). Fluid resuscitation using synthetic high molecular weight colloids has been linked to acute kidney injury, presumably due to tubular injury from osmotic nephrosis (Dickenmann, Oetli et al. 2008). However, the use of albumin for fluid resuscitation has not been linked to adverse outcomes (Finfer, Norton et al. 2004). On the other hand, the use of normal saline for volume replacement has been shown to cause hyperchloraemic metabolic acidosis, which carries a mortality risk (Bellomo, Hegarty et al. 2012).

Investigations

Recommended investigations to elicit the cause of acute kidney injury include urinalysis (urine dipstick and urine microscopy) and kidney ureter bladder ultrasonography. In addition, some patients may require a renal biopsy (KDIGO 2012). Urine microscopy has been shown to be a good predictor of acute kidney injury severity, with recognized scoring systems (Perazella, Coca et al. 2010). Findings such as red cell casts, together with the clinical picture, can aid towards making a diagnosis of crescentic glomerulonephritis, for which prompt immunosuppression is required (KDIGO 2012).

Treatment

Many patients go on to require renal replacement therapy to treat the complications (such as refractory hyperkalaemia) that cannot be managed by medical therapy alone. (KDIGO 2012).

The forms of dialysis employed in the treatment of acute kidney injury include intermittent modalities such as intermittent haemodialysis and sustained low efficiency

haemodialysis and continuous replacement therapy, such as continuous veno-venous haemodialysis and peritoneal dialysis (KDIGO 2012). Studies have found no difference in patient outcomes between the use of intermittent haemodialysis and haemodialysis involving continuous renal replacement therapy (Bagshaw, Brophy et al. 2008).

In clinical practice however, patients with haemodynamic instability, head injuries and raised intracranial pressure are managed with continuous renal replacement therapy, and those without these risk factors are treated with intermittent haemodialysis (KDIGO 2012).

Although the use of peritoneal dialysis for adults is less common in developed countries, this modality is commonly used in developing countries (Gabriel, Caramori et al. 2009). It has been demonstrated that this form of therapy can be administered in resource limited settings, such as in Moshi, Tanzania, with encouraging results (Kajiru Kilonzo, Croome 2013).

Dialysis dose

The Randomized Evaluation of Normal versus Augmented Level replacement therapy (RENAL) trial and the Veterans Affairs/National Institute of Health Acute Renal Failure Trial Network (ATN) trial looked at the intensity of continuous renal replacement therapy in critically ill patients (RENAL Replacement Therapy Study Investigators, Bellomo et al. 2009, VA/NIH Acute Renal Failure Trial Network, Palevsky et al. 2008). The RENAL trial found that no additional benefit was derived from doses higher than an effluent of 40ml/kg/hour versus 25ml/kg/hour, and the ATN trial found no added benefit from doses

of 35ml/kg/hour versus 20ml/kg/hour. Based on the above trial data, the recommended view is that the optimal dose be assigned at 20-30ml/kg/hour of dialysis effluent (KDIGO 2012).

Timing of dialysis

The optimal timing of dialysis initiation is an issue that requires further qualification (Yong, Dogra et al. 2011). From the literature review, this appears to be due to the fact that studies have looked at timing based on different categories, namely, blood urea nitrogen (BUN) levels, serum creatinine levels and the use chronological time, with conflicting results. However, the argument can be made that early initiation of dialysis translates to better patient outcomes irrespective of the category used (Palevsky 2008).

BUN and chronological time

The Project to improve Care in Acute Renal Disease (PICARD) study found that initiating dialysis at higher BUN levels was associated with higher mortality rates (Liu, Himmelfarb et al. 2006), supporting the initiation of dialysis at lower BUN levels. In contrast, the Beginning and Ending Supportive Therapy for the Kidney (BEST KIDNEY) study found that it was the duration of time before dialysis initiation that correlated to a higher mortality, rather than high BUN levels (Bagshaw, Uchino et al. 2007). This demonstrates a lack of clarity regarding the use of BUN levels to determine timing of dialysis.

Serum creatinine

The BEST KIDNEY study also found that a higher serum creatinine level at the initiation of dialysis was associated with lower mortality rates (Bagshaw, Uchino et al. 2007). This finding was seemingly paradoxical because one would expect a more severe kidney injury (and higher mortality rate), where serum creatinine levels are higher. However, this apparent paradox is explained by a study that looked at the association between survival and serum creatinine level at the start of dialysis. This study found that higher serum creatinine levels were associated with better survival (Cerda, Cerda et al. 2007). Furthermore, this finding was not affected by the nutritional status of patients (better nourished patients would be expected to have higher serum creatinine levels). Cerda, Cerda et al hypothesized that this protective effect was due to underlying chronic kidney disease, meaning that a lesser degree of acute kidney injury was required to necessitate dialysis in such patients (Cerda, Cerda et al. 2007). They also raised the possibility that a lower serum creatinine level may be due to fluid overload, which has been associated with increased mortality (Cerda, Cerda et al. 2007).

The failure of serum creatinine and BUN levels to reliably guide optimal timing of dialysis in the BEST KIDNEY study illustrated the potential shortcomings of their use as biomarkers of acute kidney injury (Bagshaw, Uchino et al. 2007).

Supportive treatment

Nutrition

It is recommended that patients with acute kidney injury receive a calorie intake of 20-30 kilocalories per kilogram per day, preferably by the enteral route (KDIGO 2012). The

importance of adequate nutrition is supported by a study by Scheikenstel et al in critically ill patients with acute kidney injury that showed an association between a negative nitrogen balance and in-hospital mortality (Scheikenstel, Kar et al. 2003) . In addition, the use of continuous renal replacement therapy itself has been shown to cause losses of amino acids, potentially contributing to a negative nitrogen balance (Hynote, McCamish et al. 1995) .

Glucose control

Glycaemic control has been extensively studied in ICU-managed medical and surgical patients. Surgical patients have been shown to benefit from the use of intensive insulin therapy to achieve tight glucose control in that this led to lower mortality rates (Van Den Berghe, Wouters et al. 2001). In contrast, intensive insulin therapy in medical patients has been associated with significant hypoglycaemia and increased mortality rates (Griesdale, de Souza et al. 2009).

Although hyperglycaemia also carries a mortality risk and ought to be treated with insulin therapy if required, it is now accepted that such treatment should not entail tight glucose control as this may be harmful in non-surgical ICU patients (KDIGO 2012, Griesdale, de Souza et al. 2009).

Outcomes of acute kidney injury:

Mortality

As previously discussed acute kidney injury with a rise in serum creatinine as small as 26.4 μ mol/l is linked to mortality (Chertow, Burdick et al. 2005, Lassnigg, Schmidlin et al. 2004). The increase in mortality correlates with the increase in severity of acute kidney injury (Thakar, Christianson et al. 2009, Chawla, Amdur et al. 2011).

The majority of the data on mortality rates in acute kidney injury is based on findings from large studies undertaken prior to the consensus definition, with figures ranging from 15%-50% (Kellum 2008). In addition, mortality rates in patients requiring dialysis were placed as high as 50% to 60% (Hoste, Schurgers 2008). However, a recent systematic review of cohort studies of acute kidney injury from 2004 to 2012, which used the KDIGO classification, reported a pooled mortality rate of 23.9% in adults (Susantitaphong, Cruz et al. 2013).

Although data on in-hospital mortality is important, following patients up at 90 days (3 months) allows detection of those who have not recovered renal function by this stage, and who, by definition, have progressed to chronic kidney disease (KDIGO 2012).

These patients are important to identify because they can be offered follow up and management to slow progression to end stage renal disease such as blood pressure control, and treatment of metabolic acidosis (Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group 2009). Additionally, should they progress to end stage renal disease, their close follow up can enable timely and safe preparation

for renal replacement therapy, in the way of a pre-emptive kidney transplant if possible, arteriovenous fistula for haemodialysis or tenckhoff catheter insertion for peritoneal dialysis (Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group 2009).

The Finnish Acute Kidney (FINNAKI) study followed up patients who were admitted in Finnish ICUs over a 12 month period in 2012, and found an overall 90 day mortality rate of 39.2% (Nisula, Kaukonen et al. 2013). This study employed the KDIGO definition of acute kidney injury (Nisula, Kaukonen et al. 2013).

Determinants of outcome

Mortality

Studies have identified elderly and paediatric patients as having worse outcomes following acute kidney injury (Cerdeira, Lameire et al. 2008, Lombardi, Yu et al. 2008). Additional contributors to poorer outcome in older patients in developing countries are multiple co-morbidities (Lombardi, Yu et al. 2008). The mortality of acute kidney injury patients with underlying chronic kidney disease has been found to be lower, presumably because smaller deteriorations in renal function are required in order to attain a severe stage of acute kidney injury in such patients (Waikar, Liu et al. 2008).

Renal recovery

The definition of renal recovery in many studies of acute kidney injury has previously been dialysis independence at the time of hospital discharge (Macedo, Bouchard et al. 2008). The ADQI group defined renal recovery as complete in cases where a patient

returns to their baseline classification within the RIFLE criteria. Partial renal recovery was attributed to patients who have a persistent deterioration in classification but are not dialysis dependent. End stage renal disease was diagnosed if patients remained dialysis dependent after 3 months (Bagshaw, Laupland et al. 2005). Reports from the study by Ali et al, which was a population study, found that 92.5% of surviving patients had full renal recovery, 7% had partial renal recovery and 0.6% had no recovery (Ali, Khan et al. 2007).

Identification of gaps and needs for further research

This review of existing literature on acute kidney injury has led to an identification of areas requiring further research. A useful study would be one that looks at the effect of simple, protocol based clinical scoring systems in developing countries. These scoring systems can be used to alert clinicians to patients at risk of acute kidney injury, thus providing an opportunity for early intervention.

Another area of research could be one that replicates and expands on the study by Markota et al. As previously discussed, this study was important in that it demonstrated a benefit in achieving a urine alkalinity of pH of >6, for protecting against contrast induced nephropathy. This level of urine alkalinity was hypothesized to protect against the formation of free-radicals in the renal medulla. Previous studies of the role of alkalisation (using sodium bicarbonate) have shown mixed results. A possible explanation for this discrepancy may be that unlike in the study by Markota et al, the

urine alkalinity was not assessed and therefore ineffective doses of bicarbonate may have been administered.

Lastly, the literature review has demonstrated that further studies on the optimal timing of renal replacement therapy are still required. This is especially the case where patients may not fulfill the traditional indications for initiation of dialysis, but may have otherwise benefitted from early dialysis.

Aims and Objectives

- To investigate the epidemiology of acute kidney injury at Groote Schuur Hospital.
- To investigate the management of acute kidney injury at Groote Schuur Hospital.
- To identify possible preventive measures in the development of acute kidney injury in the Groote Schuur Hospital setting.
- To investigate the outcome of patients with acute kidney injury in terms of 90 day mortality, progression to chronic kidney disease and level of recovery of renal function.
- To determine if timing of dialysis affects patient outcome.

Methods

Study Design

A prospective cohort study of patients referred to Groote Schuur Hospital Renal Unit with acute kidney injury from the 8th of July 2012 to the 8th of July 2013.

Setting

The study was carried out at the Renal Unit of Groote Schuur Hospital, Cape Town, South Africa. The hospital hosts one of the largest referral based, state-sector renal units in sub-Saharan Africa.

Eligibility Criteria

Inclusion criteria

Patients with native (non-transplant) kidneys who were above the age of 13 and referred to the renal unit with acute kidney injury were eligible if they fulfilled the KDIGO definition of acute kidney injury. The study included patients referred from the medical, surgical and obstetrics and gynaecology disciplines. We included patients managed in the ICU and patients with all 3 stages of acute kidney injury.

Acute kidney injury diagnosis

Where baseline serum creatinine was not known, patients who went on to demonstrate an improvement in serum creatinine (independent of dialysis) were deemed to have undergone an episode of acute kidney injury. We did not employ the use of an estimated baseline serum creatinine based on the Modification of Diet in Renal Disease (MDRD) study equation, as has been done in other studies (This is further discussed under the section entitled 'study limitations' in this paper).

Patients with no known pre-existing serum creatinine level were staged according to the level of recovery in serum creatinine. In addition, all patients in whom renal replacement therapy was initiated were staged under stage 3 acute kidney injury, according to the KDIGO classification.

Exclusion criteria

The cohort excluded children under the age of 13 who would have been referred to the nearby Red Cross Children's Hospital. Other patients excluded included those on renal replacement therapy and patients with serum creatinine levels higher than 354 μ mol/l at baseline.

Study Procedures

Patient details were obtained from doctors rotating through the renal unit. Patients were then located and data collected retrospectively from the clerking sheet designed to incorporate information required as a basic standard for patients with acute kidney injury. This clerking sheet also served as a data capture sheet (Appendix 2). Further and missing data was retrospectively obtained from the electronic laboratory database and hospital record database. Patients were contacted at or after three months (ninety days) following the acute kidney injury episode, to present themselves for a repeat serum creatinine level. Electronic laboratory details were also sought for three month or post three month creatinine levels for patients who were not able to return for follow up. Patients who had abnormal serum creatinine levels were referred for follow up in the Renal Unit.

Patients in whom acute kidney injury developed during their hospital admission were deemed to have hospital acquired acute kidney injury. Patients with abnormal results on admission, as well as those whose presenting conditions on admission are known to predispose to community acquired acute kidney injury (such as gastroenteritis), were

labeled as having community acquired acute kidney injury. This included patients referred from secondary and primary level institutions.

Data Collection and management

Data collection instrument

Primary data was entered onto a data collection form designed to be used by clinicians when seeing patients. This clerking sheet collected data on patient demographics, clinical status, patient management, laboratory results and outcome measures. Confirmation of data on patient ethnicity was obtained from hospital records. Data was then recorded on an Excel spreadsheet.

Demographic and Epidemiological data

This included patient age, gender, and ethnicity. Information collected also included past medical history, habits, and reason for admission, as well as risk factors for acute kidney injury. Epidemiological data included information on patient illness severity.

Not all patients had the required data to enable the use of the Acute Physiology and Chronic Health Evaluation (APACHE) scoring system. The decision was therefore made to utilize the acute kidney injury stage (assigning clinical severity to stage 3) as a surrogate marker of patient clinical severity. This marker has previously been shown to correlate with the clinical state and outcome of patients with acute kidney injury (Barrantes, Tian et al. 2008, Ostermann, Chang 2009). The data collected also included potential causes of acute kidney injury such as trauma, sepsis, toxins (herbal and synthetic), obstetric causes, intrinsic renal, pre-renal and obstructive causes. Data on

potential risk factors and associations with acute kidney injury, such as hypertension, diabetes mellitus, chronic kidney disease, heart disease, and substance abuse was also collected.

Management data

Management data included the department referring the patient (medicine, surgery or obstetrics and gynecology), whether the patient was managed in the ICU or not, whether the patient received dialysis or not, whether investigations included fluid balance, urine output, urine dipstick, urine microscopy, kidney ureter bladder ultra sound scan, or renal biopsy, and whether patients were mechanically ventilated or on inotropes.

Dialysis data

The investigators collected data on the dialysis modality employed. A number of patients inter-changed the dialysis modalities and were considered under the first dialysis mode used. Time to dialysis initiation from the diagnosis of acute kidney injury was measured for each patient in days.

Outcome data

The investigators considered two outcomes, namely mortality and recovery of renal function.

- Mortality was measured at two intervals - at 30 days and at 90 days. This was a binary (alive/dead) outcome.
- Recovery of renal function was measured using two criteria. These were independence from dialysis, and the return of serum creatinine levels to within 1.5 times the patient's baseline at three months follow-up. In patients with no known

baseline creatinine the investigators used the “normal” National Health Laboratory Service range of 41-90 μ mol/l. Our definition of renal recovery was based on that of the ADQI group, where full renal recovery is return to the baseline RIFLE classification (serum creatinine less than a multiple of 1.5 from baseline), partial recovery if patients persist at a more severe RIFLE class but are not dialysis dependent, and End stage renal disease if they are dialysis dependent after three months (Bagshaw, Laupland et al. 2005). Where the baseline serum creatinine level was unknown, patients whose renal function recovered to a level within the laboratory reference range were assessed as fully recovered.

Data management and validation

Data was retrospectively entered into an Excel spreadsheet from the clerking sheet. The data was entered onto the spreadsheet by the principal investigator and assistants. Attempts were made to find missing data from laboratory records and the patients' hospital records. Outliers were double-checked with patient records.

Statistical Considerations

The data in the excel spreadsheet was cleaned and imported into Stata 12.1 for analysis (Stata Corporation, College Station, TX, USA). All statistical analyses were carried out using Stata 12.1. All statistical hypotheses were carried out at a 5% level of significance and 95% confidence intervals (CI) were reported.

Categorical data

Proportions were described and the chi squared test and its variants was used to test associations.

Continuous data

The data was tested for *normality* using the Shapiro-Wilks test. For *normally* distributed data, means and standard deviations were described while medians and interquartile ranges (IQR) were described for *non-normally* distributed data.

The investigators used the *t-test* and its variants to test associations between *normally* distributed variables and groups while the Mann-Whitney U test and its non-parametric variants was used to test associations in *non-normally* distributed data.

Analysis of potential associations with mortality

The investigators used Odds Ratios (OR), P-values and 95% confidence intervals to describe associations. Univariate relationships between potential determinants of mortality at 3 months were tested and reported. Epidemiological variables, co-morbidities and management variables were considered.

Multivariate analysis of determinants of mortality at 3 months was carried out using forward stepwise logistic regression, with a 0.05 significance level for addition and a 0.15 significance level for removal of variables. The investigators included variables with a P-value of less than 0.20 from the univariate analysis. Demographic variables considered as confounders were age, gender and ethnicity.

Further analysis included dialyzed patients only. The effect of the timing of dialysis was explored, with the time (days) to dialysis from acute kidney injury onset categorized into early (1 day), delayed (2 – 5days) and late (>5 days). This categorization of timing of

dialysis was based on that used in the BEST KIDNEY study (Bagshaw, Uchino et al. 2007). Day 1 was the day of admission.

Ethical Considerations

Ethical approval was sought and granted by the University of Cape Town Human Research Ethics Committee. The data collection instrument was a clerking sheet designed for the study and subsequently used in standard practice. However, as the study did not involve further intervention in addition to standard patient management by the doctors in the Renal Unit, the need for patient consent was waived.

RESULTS

EPIDEMIOLOGY

Demographics

We included a total of 366 patients from the 8th of July 2012 to the 8th of July 2013 (Table 1). Of these 214 (58.5%) were male. The ethnic distribution was comprised of 183 (50%) Coloured patients, 146 (39.9%) Black, 35 (9.6%) White, and 2 (0.5%) were classified as Other (Table 1).

The median age was 44 (IQR 14 – 82). The 41-65 age category had 156 patients (42.6%), followed closely by the 19-40 category with 143 (39.1%) of the patients, while there were 57 patients (15.6%) aged 66 and older, and only 10 patients (2.7%) aged 18 or younger (Table 1).

The source of acute kidney injury was community acquired for 265 patients (72.4%), while 101 (27.6%) had hospital acquired acute kidney injury (Table 1).

Medical referrals were made up of 217 patients (59.3%), followed by 124 (33.9%) surgical patients and 25 (6.8%) obstetrics and gynaecology patients (Table 1).

Amongst the 124 patients referred from the surgical department, 66 (18.0%) had non cardiovascular surgery, and 30 (8.2%) had cardiovascular surgery. Of the 25 referred from the obstetrics and gynecology departments, 4 (1.1%), had surgery (Table 1).

The number of patients with stage 3 acute kidney injury disease was 307 (83.9%) (Table 1).

Of the 101 patients with hospital acquired acute kidney injury, 72 (71.3%) had stage 3 acute kidney injury (Table 9).

Table 1 – Demographic data, N = 366

Variable	Total	(%)	Mean	Range	SD	Median	IQR
<u>Age</u>							
Age (years)			45.6	13-91	16.6	44	14-82

≤ 18 years	10	2.7%
19-40 years	143	39.1%
41-65 years	156	42.6%
≥ 66years	57	15.6%

Gender and ethnicity

Male	214	58.5%
Female	152	41.5%
Coloured	183	50.0%
Black	146	39.9%
White	35	9.6%
Other	2	0.5%

Referring discipline

Medical	217	59.3%
Surgical	124	33.9%
Obs/Gyn	25	6.8%

Surgical procedure

*CV surgery	30	8.2%
*Obs/gyn surgery	4	1.1%
*Gen/orth surgery	66	18.0%

<u>*AKI source and stage</u>		
Community AKI	265	72.4%
Hospital AKI	101	27.6%
AKI stage 1	27	7.4%
AKI stage 2	32	8.7%
AKI stage 3	307	83.9%

*(AKI – acute kidney injury, CV – cardiovascular, Gen/Orth – general or orthopaedics, Obs/Gyn – obstetrics and gynaecology)

Risk factors

Hypertension was the most common co-morbidity and was present in 152 (41.9%) of the patients. Other co-morbidities included diabetes mellitus in 65 (17.8%), heart disease in 58 (16.1%), trauma in 41 (11.2%), mycobacterium tuberculosis (TB) in 20 (5.5%), pregnancy in 17 (4.5%) and cancer in 16 (4.4%) including 3 (0.82%) with multiple myeloma. The number of patients with HIV was 75 (20.6%) (Table 2). Of the HIV positive patients, 46 (61.3%), were in the 19-40 years age range (Table 2). Overall prior chronic kidney disease was identified in 37 (10.1%) patients, including 10 (2.7%) patients with HIV associated nephropathy (Table 2).

Table 2 – Acute kidney injury risk factors and co-morbidities

Variable	Total (%)
Hypertension	152 (41.5)
HIV	75 (20.6)
<u>HIV and age category in years, N (%)</u>	
- 0-18	0
- 19-40	46 (61.3)
- 41-65	27 (36.0)
- ≥ 66	2 (2.7)
Diabetes mellitus	65 (17.8)
Heart disease	58 (16.1)
Chronic kidney disease	37 (10.1)
- including biopsy proven HIVAN	- 10 (2.7)
Active TB	20 (5.5)
Pregnancy	17 (4.6)
Cancer	16 (4.4)
Cerebrovascular disease	8 (2.0)

Associations and causes of acute kidney injury

Sepsis was present in 222 (60.7%) patients. It was either the sole cause or one of the causes of acute kidney injury in patients who had more than one potential cause (Table

3). Of the 101 patients with hospital acquired acute kidney injury 63 (62.4%) had sepsis (Table 9).

A biopsy proven diagnosis of acute kidney injury was obtained in 36 (9.8%) of the patients (Table 4 and Appendix 3).

Acute tubular necrosis was the most common underlying cause of acute kidney injury, present in 272 (72.1%) of the patients (Table 4). Pre-renal causes of acute tubular necrosis included gastroenteritis, vomiting and dehydration in 47 (12.8%) patients, and 4 (1.1%) from obstetric haemorrhage (Table 3). A total of 137 (37.4%) patients had acute tubular necrosis secondary to exogenous nephrotoxins. These included 7 (1.9%) due to herbal medication, 23 (6.3%) due to tenofovir, 10 (2.7%) due to aminoglycosides, and 50 (13.7%) due to intravascular iodine based radiocontrast agents (Table 4).

Additional intrinsic renal causes of acute kidney injury included 20 (5.5%) due to glomerulonephritis (including one clinical diagnosis), 19 (5.2%) due to acute interstitial nephritis, 19 (5.2%) due to pyelonephritis, and 7 (1.9%) due to malignant hypertension. A thrombotic cause was identified in 1 (0.27%) patient with renal infarcts. Acute kidney injury due to obstruction was identified in 17 (4.6%) patients (Table 4 and Appendix 3).

Among the Obstetrics and gynaecology patients compared to the total study population, 14 (3.8%) had pre-eclampsia and 1 (0.27%) presented following a septic abortion (Table 3).

A total of 96 (26.2%) patients developed acute kidney injury in relation to a surgical procedure (Table 1). In addition, 41 (11.2%) had trauma as a cause, including 5 (1.4%)

with crush syndrome secondary to mob violence (Tables 3 and 4). A total of 16 (4.4%) patients presented following acute pancreatitis, and in 4 (1.1%) of these the cause was alcohol (Table 3).

A total of 305 (83.3%) patients had a single presumed or known histological cause of acute kidney injury, but 61 (16.7%) had more than one known or presumed histological cause (Table 1).

Table 3 – Precipitants/causes of acute kidney injury

Variable, N (%)	Total (% of the total of 366 patients in the study unless otherwise specified)
<u>Sepsis (as either the sole cause or one of the causes)</u>	<u>222 (60.7%)</u>
- pneumonia	- 42/222 (18.9%)
- pyelonephritis/urosepsis	- 27/222 (12.2%)
- sepsis post trauma	- 24/222 (10.8%)
- acute gastrointestinal tract pathology*	- 24/222 (10.8%)
- soft tissue	- 6/222 (2.7%)

- bacterial gastroenteritis	- 4/222 (1.8%)
- meningitis	- 2/222 (0.9%)
- septic arthritis	- 2/222 (0.9%)
- septic abortion (also included later in this table)	- 1/222 (0.5%)
- other	- 90/222 (40.5%)
<u>Toxins</u>	<u>137 (37.4%)</u>
- IV contrast	- 50 (13.7%)
- Tenofovir	- 23 (6.3%)
- Aminoglycosides	- 10 (2.7%)
- Herbal toxins	- 7 (1.9%)
- Other exogenous toxins	- 47 (12.8%)
Gastroenteritis/vomiting/dehydration	47 (12.8%)
Cardiovascular surgery related	30 (8.2%)
Non cardiovascular, non obstetric surgery related	66 (18.0%)
Trauma	41 (11.2%)
Pancreatitis	16 (4.4%)
Abdominal compartment syndrome	1 (0.27%)
Pre-eclampsia	14 (3.8%)
Obstetric haemorrhage	4 (1.1%)
Septic abortion	1 (0.27%)
Obstruction	17 (4.6%)

Thromboembolic (renal infarction)	1 (0.27%)
Multiple myeloma	3 (0.82%)
Intrinsic renal – see Table 4 for clinically and histopathologically determined causes of acute kidney injury	

(*Includes – primary esophageal, gastric, pancreatic, intestinal, and biliary tract sepsis)

*Table 4 – Pathological diagnoses of acute kidney injury including biopsy proven cases
(Full patient data on renal biopsy findings is in Appendix 3)*

Variable	Total (%)
<u>ATN predominant</u>	<u>272 (72.1%)</u>
- ATN only	- 260
- From rhabdomyolysis	- 11
- (Rhabdomyolysis from mob violence)	- 5
- With other acute (myeloma + pyelonephritis)	- 1

<u>Acute interstitial nephritis</u>	<u>19 (5.2%)</u>
- Predominant	- 14
- Granulomas (excluding other granulomas)	- 5
<u>Pyelonephritis</u>	<u>19 (5.2%)</u>
- alone	- 12
- with other	- 7
<u>TMA</u>	<u>9 (2.5%)</u>
- Malignant hypertension	- 7
- *Other TMA	- 2
Multiple myeloma (including 1 with pyelonephritis +ATN)	3 (0.82%)
Glomerulonephritis (includes 1 clinical diagnosis)	20 (5.5%)
Pre-eclampsia	14 (3.8%)
Obstruction	17 (4.6%)

*(TMA – thrombotic microangiopathy)

PREVENTION AND MANAGEMENT

A total of 202 (55.2%) patients were managed in ICU, while 204 (60.7%) were dialysed (Table 5). Of the 204 dialysed patients, 5 did not have a clear record of the first dialysis modality, having had more than one dialysis modality. Of the 199 patients who did have data on first dialysis modality, 88 (44.2%) were on intermittent haemodialysis, while 72

(36.2%) were on sustained low efficiency dialysis, and 39 (19.6%) were on continuous veno-venous haemodialysis (Table 5). A total of 145 (39.6%) patients had both ICU admission and dialysis (Table 5).

Only 195 (53.3%) patients had a documented 24 hour urine output, and 140 (38.3%) had a fluid input charted. A total of 100 (27.3%) patients had a documented urine dipstick result, and urine microscopy was done in 29 (7.9%) patients. A total of 90 (24.6%) patients had a kidney ureter ultrasound scan around the time of presentation (Table 5).

Table 5 – Patient management

Variable	Total	(%)
ICU admission	202	55.2%
Mechanical ventilation	107	29.2%
Inotropes	84	23.0%
Total Dialysed*	204	55.7%

*(Dialysis modality – note that 5 patients had unclear data on first dialysis modality, therefore percentages are out of a total of 199 patients who had clear first dialysis modality)

First dialysis IHD*	88	44.2%
First dialysis SLED*	72	36.2%
First dialysis CVVHD*	39	19.6%
Dialysis and ICU	145	39.6%
24 hour urine output	195	53.3%
- [$<500\text{ml}/24\text{ hours} = 113/195 (57.9\%)$]		
24 hour fluid input	140	38.3%
Urine dipstick	100	27.3%
Urine microscopy	29	7.9%
KUB ultrasound scan	90	24.6%

*(IHD – intermittent haemodialysis, SLED –sustained low efficiency haemodialysis, CVVHD – continuous veno venous haemodialysis, KUB – kidney ureter bladder)

Timing of dialysis

The mean time to dialysis was one day (IQR 1-2, Range 1-21) (Table 7). Among the 119 patients returning for 3 month follow up, a total of 55 (46.2%) had dialysis. Of these, 51 (92.7%) had early dialysis (Table 12).

OUTCOMES

Mortality

The overall 90 day mortality rate was 38.8% (142 patients), and the 30 day mortality rate was 31.2% (114 patients) (Table 6).

An increase in the proportion of both 30 and 90 day mortality was seen with increasing severity stage of acute kidney injury. However, although this showed an association with 90 day mortality on univariate analysis (OR 1.70, p-value 0.015, 95% CI 1.11-2.61), multivariate analysis did not identify it as an independent predictor of mortality (Tables 6 and 7). Both 30 and 90 day mortality rates were higher among surgical patients (36.3% and 46.8% respectively) (Table 6). Univariate analysis showed a mortality association with surgical admissions (OR 1.65, p-value 0.026, 95% CI 1.06-2.57) but not multivariate analysis (Table 7).

The 90 day mortality of patients managed in the ICU was 45.5% (92 of 202) rising to 49.0% (71 of 145) in those who were both dialysed and managed in ICU (Table 6).

Mortality rates increased with increasing patient age, and univariate analysis showed a mortality association with increasing age (OR 1.02, p-value 0.021, 95% CI 1.00-1.03). However on multivariate analysis, age was not an independent predictor of mortality (Table 7).

There was no significant difference in the mortality rates among the different age categories for patients who were managed in ICU (p-value 0.484), those who were dialysed (p-value 0.400), or those who were both managed in ICU and dialysed (p-value 0.484) (Table 8).

Both SLED and CVVHD had a mortality association on univariate analysis (OR 2.04, p-value 0.007, 95% CI 1.21-3.44) and (OR 2.51, p-value 0.008, 95% CI 1.28-4.94) respectively, but they were not independent predictors of mortality on multivariate analysis (Table 7).

Although HIV was found in 20.6% of the patients, it did not carry an association with 90 day mortality on univariate analysis (OR 1.07, p-value 0.801, 95% CI 0.64-1.80) (Table 7).

On multivariate analysis, mechanical ventilation was the only independent predictor of 90 day mortality (OR 2.46, p = 0.019, 95% CI 1.41-4.30), (Table 7). However, a borderline association with mortality was seen with sepsis (OR 1.83, p = 0.066, 95%CI 1.02-3.27), and prolonged time to dialysis (OR 1.93, p = 0.080, CI 0.93-4.03) (Table 7).

Among patients with hospital acquired acute kidney injury, sepsis was present in a greater proportion of those who were dead at 90 days compared to those who were alive (p-value 0.005) (Table 9). Of the 50 patients with hospital acquired acute kidney injury who were dead at 3 month follow up 39 (78%) had stage 3 acute kidney injury (Table 7).

Table 6 – 30 and 90 day mortality and associated patient characteristics

Variable	30 day mortality, N (%)				90 day mortality, N (%)			
	Medical	Surgical	Obs/Gyn	Overall	Medical	Surgical	Obs/Gyn	Overall
	N = 217	N = 124	N = 25	N = 366	N = 217	N = 124	N = 25	N = 366

Total	67 (30.9)	45 (36.3)	2 (8.0)	114/366 (31.2)	81 (37.3)	58 (46.8)	3 (12.0)	142/366 (38.8)
Dialysed	48/120 (40.0)	28/73(38.4)	1/12 (8.3)	77/205 (37.6)	56/120 (46.7)	37/73 (50.7)	3/12 (25.0)	96/205 (46.8)
ICU/dialysed	30/72 (41.7)	28/66 (42.4)	1/7 (14.3)	59/145 (40.7)	31/72 (43.1)	37/66 (56.1)	3/7 (42.9)	71/145 (49.0)
ICU	34/89 (38.2)	43/105 (41.0)	1/8 (12.5)	78/202 (38.6)	35/89 (39.3)	54/105 (51.4)	3/8 (37.5)	92/202 (45.5)
AKI 1				2/27 (7.4)				4/27 (14.8)
AKI 2				9/32 (28.1)				12/32 (37.5)
AKI 3				103/307 (33.6)				126/307 (41.0)

Table 7 – Univariate analysis of potential risk factors for 90 day mortality and multivariate analysis

Variable	Univariate analysis			Multivariate analysis		
	OR	p-value	95%CI	OR	p-value	95%CI

<u>Demographics</u>			
Age	1.02	0.021	1.00-1.03
Surgical 58/124 (46.8%)	1.65	0.026	1.06-2.57
<u>Risk factors/associations</u>			
Sepsis 102/222 (45.9%)	2.21	0.001	1.41-3.47
Hypertension 61/152 (40.1%)	1.10	0.669	0.72-1.68
HIV 30/75 (40.0%)	1.07	0.801	0.64-1.80
Acute kidney injury stage	1.70	0.015	1.11-2.61
<u>Management</u>			
Dialysis 96/204 (47.1%)	2.24	<0.001	1.45-3.47
ICU 92/202 (47.5%)	1.89	0.004	1.23-2.93
Dialysis + ICU 74/145 (51.0%)	2.06	0.001	1.33-3.17
First SLEDD 38/72	2.04	0.007	1.21-3.44
First CVVHD 23/89	2.51	0.008	1.28-4.94
First HD 34/88	0.99	0.972	0.61-1.62
Mech vent 58/107	2.76	<0.001	1.69-4.51
Inotropes 43/84	2.27	0.001	1.37-3.76
Time to dialysis (Median time 1, IQR 1-2, Range 1-21)	1.14	0.073	0.99-1.32
	1.83	0.066	1.02-3.27
	2.46	0.019	1.41-4.30
	1.93	0.080	0.93-4.03

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Table 8 – Mortality in ICU managed and dialysed patients according to age category

	0-18	19-40	41-65	≥ 66	p-value
	N = 10	N = 143	N = 156	N = 57	
All	2 (20.0)	46 (32.2)	67 (43.0)	27 (47.4)	0.071
Dialysis	2 (20.0)	32 (22.4)	47 (30.1)	15 (26.3)	0.400
ICU + dialysis	2 (20.0)	22 (15.4)	38 (24.4)	9 (15.4)	0.498
ICU	2 (20.0)	27 (18.9)	48 (30.8)	15 (26.3)	0.484

Table 9 – Characteristics of patients with Hospital Acquired acute kidney injury, and 90 day mortality, Total = 101

Variable	Dead N = 50	Alive N = 51	Total	p-value

N/101 (%)				
Sepsis	38 (76.0%)	25 (49.0%)	63/101 (62.4)	0.005
Dialysis	30 (60.0%)	17 (33.3%)	47/101 (46.5)	0.00739
AKI stage 3	39 (78.0%)	33 (64.7%)	72/101 (71.3)	0.018
AKI stage 2	0 (20.0%)	8 (15.7%)	8/101 (7.9)	
AKI stage 1	1 (2.0%)	10 (19.6%)	11/101 (10.9)	
Fluid balance	26 (52.0%)	28 (54.9%)	54/101 (53.5)	0.613
Urine output recorded	32 (64.0%)	28 (54.9%)	60/101 (59.4)	0.365
Contrast	9 (18.0)	9 (17.7%)	18/101 (17.8)	0.963

Renal recovery

Of the 224 patients who were alive at 3 months, a follow up serum creatinine at 90 days or more, was available in only 119 (53.1%) of the patients. Of these, complete renal recovery occurred in 95 (80.5%) patients and 4 (3.4%) went onto end stage renal disease (Table 11).

Of the 57 patients who were managed in ICU but not dialysed, 47 (82.5%) had full renal recovery. Among the 40 patients who were admitted to ICU and dialysed, and who had a follow up serum creatinine, 31 (77.5%) had full renal recovery (Table 10).

Only 18 (69.2%) of the 26 patients with HIV had full renal recovery on follow up at 3 months (Table 10).

Of the 4 patients who went on to end stage renal disease, 3 were aged 19-40 (Table 11), 2 were HIV positive and 3 had been managed in the intensive care unit.

Additionally, all 4 of them had had sepsis and dialysis (Table 10). (Long term renal replacement therapy was offered for 2 of the patients with end stage renal disease, including one who was HIV positive. One patient was lost to follow up and one absconded).

Of the patients with a follow up serum creatinine at 90 days or more, all those aged 18 or younger had full renal recovery, but only 31 (68.9%) of those aged 19-40 years had full renal recovery, with 31 out of 45 (68.9%). This was in contrast to full renal recovery in 86.5% of those aged 41-65 years, and in 84% of those aged 66 years and older (Table 11).

Table 10 – Predictors of renal recovery in patients with 3 month (90 day) followed up, N=119

Variable	Yes, N =95	Partial, N =20	No, N = 4	p-value

Sepsis, N (%)	48 (50.5)	12 (60.0)	4 (100)	0.002
ICU, N (%)	47 (49.5)	7 (35.0)	3 (75.0)	0.018
Dialysed, N (%)	42 (44.2)	9 (45.0)	4 (100)	0.001
ICU,dialysis, N (%)	31 (32.6)	6 (30.0)	3 (75.0)	0.022
HIV, N (%)	18 (50.5)	6 (30.0)	2 (50.0)	0.383

Table 11 – Renal recovery and age category, N= 119

Age range	Full recovery	Partial recovery	No recovery	Total
0-18 y	3	0	0	3
19-40	31	3	11	45
41-65	45	1	6	52
≥ 66	16	0	3	19
Total	95	4	20	119

Table 12 – Comparison between patients followed up at 3 months and those lost to 3 month follow up

	Followed up, N =119	Not followed up, N = 105	p-value
value			

	(dialysed = 55/119 (46.2%))	(dialysed = 53/103 (50.5%))	
Age, median (IQR)	44 (35-59)	39 (30-55)	
			0.049
Ethnicity, N (%)			
			0.982
Coloured	61 (51.3%)	51 (50.4%)	
Black	47 (39.5%)	44 (40.7%)	
White	10 (8.4%)	9 (8.0%)	
Other	1 (0.84%)	1 (0.88%)	
Sepsis, N (%)	64 (53.8%)	56 (53.3%)	0.946
Mech vent, N (%)	34 (28.6%)	15 (14.3%)	0.017
ICU, N (%)	58 (48.7%)	53 (44.5%)	
			0.640
Dialysis, N (%)	55 (46.2%)	53 (50.5%)	0.525
Early dialysis, N (%)	51/55 (92.7%)	45/53 (84.9%)	
			0.254

DISCUSSION

Epidemiology

Incidence

We conducted a prospective observational study of the patient population at Groote Schuur Hospital, a tertiary institution in South Africa, to investigate the epidemiology, management and outcomes of acute kidney injury. The overall incidence of acute kidney injury was derived from the total number of non-private patient hospital admissions to the institution for the period 2011-2012. The number of admissions was 44,285, equating to an incidence proportion of 0.83% (Appendix 4).

This incidence proportion is low compared to recent reports from developed countries where the incidence is rising (Waikar, Liu et al. 2008). A possible reason may be that this figure is an under-estimate of the true incidence of acute kidney injury in the hospital and may be explained by the low referral of patients to the Renal Unit.

Ethnicity and age

The ethnic distribution of the patients in our study mirrored that of the Western Cape, which is predominantly made up of Coloured patients, closely followed by Black patients and fewer White patients (Statistics South Africa. Mid-year Population Estimates, 2013).

Our finding of a mean patient age of 45.6 was slightly younger than the age noted in a study on medical admissions to Groote Schuur Hospital by Myer et al, which reported a

mean age of 49 in 2009 (Myer, Smith et al. 2013). The age range (13-91) in our study included both young adults and elderly patients and differed from the trends seen in other developing countries, where acute kidney injury is reported to affect mainly young patients (Cerda, Cerda et al. 2007, Cerda, Lameire et al. 2008, Cerdá, Bagga et al. 2008, Cerdá, Bagga et al. 2008).

We found that there were more male than female patients with acute kidney injury. This pattern differs from the Western Cape demographics, where there is a slight female predominance at 51.9% (Statistics South Africa. Mid-Year Statistical Estimates,2013). Based on this demographic statistic, one would expect to see more female patients presenting at the hospital. This expectation would also be in keeping with previous studies of adult patients with acute kidney injury conducted worldwide which tend to show a predominance of female patients (Liano, Pascual 1996, Bagshaw, Uchino et al. 2007).

Risk factors

We found that patient risk factors for acute kidney injury reflected a combination of those found in both developed and developing countries. These consisted of non-communicable diseases (such as hypertension, diabetes mellitus, and heart failure), obstetric causes and infectious diseases (HIV and tuberculosis).

We also found that a large proportion of the patients (41.5%) we studied had hypertension as a risk factor. Hypertension is a potential cause of chronic kidney disease, which is a recognized risk factor for acute kidney injury (Lafrance, Djurdjev et

al. 2010). Our finding may be due to the increasing prevalence of this condition in the South African population (Naicker 2009).

We also note that the proportion of patients with HIV (20.6%) was higher than the national prevalence of HIV in South Africa, which was placed at 10% in the 2011/2012 census, published in May 2013 (Statistics South Africa. Mid-Year Statistical Estimates,2013). Our finding may be explained by the fact Groote Schuur Hospital is a tertiary centre that receives referrals from both secondary and primary level health facilities, including severely ill HIV positive patients.

Source of acute kidney injury

Patients were referred from the medical discipline (59.3%), the surgical discipline (33.9%) and the obstetrics and gynaecology department (6.8%). The low percentage of obstetric and gynaecology cases may be due to national efforts to improve maternal and child health care (Li, Burdmann et al. 2013).

Similarly to other developing countries, the majority of patients (72.4%), had community acquired acute kidney injury (Cerdá, Bagga et al. 2008). Although patients with hospital acquired acute kidney injury were in the minority (27.6%), the majority of these patients (71.3%) had stage 3 acute kidney injury and sepsis (62.4%). This high percentage may be explained by a delay in detection of deterioration in the clinical condition of hospitalized patients, resulting in late referral.

Causes

We found that sepsis was the most common cause of acute kidney injury across all the referring disciplines (60.7%). Among patients who had community acquired acute kidney injury this may be a reflection of the burden of communicable diseases in South Africa. Among patients with hospital acquired acute kidney injury, this may reflect the rates of nosocomial infections in the hospital, such as *Acinetobacter baumannii* in the ICU setting (Gounden, Bamford et al. 2009) .

The proportion of patients with obstruction (17%) is comparable to that found in studies conducted in Sudan, where the percentage of patients in whom obstruction was a cause of acute kidney injury ranged from 12.3% to 27.9% (Elsharif, Ibrahim et al. 2010, Kaballo, Khogali et al. 2007). While the percentage in our study is significant, it is important to note that a kidney ureter bladder ultrasound scan, which plays an important role in the initial exclusion of obstruction, was only performed on 29% of the 366 patients included in the study.

A histopathological cause of acute kidney injury was obtained in 36 (9.6%) patients who had a renal biopsy. The histopathological diagnosis was used to guide the management and prognostication of the patients. The diagnoses included glomerulonephritis in 19 patients and granulomas (in combination with other findings) in 8 patients. While a key difference in our study was the frequent detection of mesangiocapillary glomerulonephritis and granulomas, these histopathological diagnoses were similar to those found in the studies by Liano et al in Spain, and Kaballo et al in Sudan (Kaballo, Khogali et al. 2007, Liano, Pascual 1996).

Our study therefore found that causes of acute kidney injury in our patient population included those common to developing countries (such as herbal toxins, glomerulonephritis, and gastroenteritis) , as well those common to developed countries, (such as post surgery and iodine based radio-contrast) (Naicker, Aboud et al. 2008, Cerdá, Bagga et al. 2008).

Management

Our findings show that the overall percentage of patients who received dialysis was 55.7%. We also found that 51% of ICU admissions presenting with acute kidney injury received dialysis. This finding of a high percentage of ICU managed patients treated with dialysis was similar to the experience of urban areas of other developing countries (Cerdá, Bagga et al. 2008)

This study found that the most commonly used first dialysis modality was intermittent haemodialysis (44.2%). This was followed by slow low efficiency dialysis (36.2%) and continuous veno-venous haemodialysis (19.6%). This differs from the experience in other developing countries where peritoneal dialysis is the most common modality (Gabriel, Caramori et al. 2009).

Although both sustained low efficiency dialysis and continuous veno-venous haemodialysis were associated with mortality on univariate analysis (OR 2.04) and (OR 2.51) respectively, they were not independent predictors of mortality on multivariate analysis. A multicentre prospective randomized controlled trial of ICU patients with acute kidney injury, by Lins et al found no difference in outcome between patients

treated with intermittent or continuous renal replacement therapy (Lins, Elseviers et al. 2009). However the use of continuous renal replacement therapy has been associated with better fluid removal than intermittent renal replacement therapy, which is important because fluid overload in patients with acute kidney injury carries a mortality risk (Bouchard, Soroko et al. 2009). Furthermore, there is evidence for better renal outcome in inotrope dependant patients with acute kidney injury who are treated with continuous renal replacement therapy, in that fewer of them go on to require chronic dialysis compared to those who are treated with intermittent renal replacement therapy (Prowle, Bellomo 2010).

Our study illustrated that not many patients received basic bedside investigations and management in the form of fluid balance charts, urine dipsticks and urine microscopy, which are key in making the diagnosis of acute kidney injury (KDIGO 2012). This may be explained by staffing issues, especially in the general, non-ICU wards, which typically have higher patient to medical staff ratios.

Prevention

One of the aims of the study was to identify potential areas of prevention of acute kidney injury. In our study, the majority of patients with hospital acquired acute kidney injury had stage 3 disease (71.2%), suggesting that the opportunity for earlier intervention to prevent progression from less severe disease was missed.

A large proportion of these patients (62.4%) also had sepsis, which was associated with mortality (p-value 0.005). It may be that earlier detection and management of sepsis in these in-hospital patients could have prevented the development of acute kidney injury.

Prevention and early detection are essential in reducing acute kidney injury related mortality. It is therefore imperative that clinicians are aware of high risk patients. This is especially important when one considers the high cost of renal replacement therapy in developing countries (Anathhanam, Lewington 2013).

Outcome

Mortality

Our study found that 80.3% (114/142) of patients died within 30 days of acute kidney injury diagnosis. The overall 90 day mortality rate of 38.8% was slightly lower than that reported by Ali et al of 41%, in a population that included patients with the full spectrum of acute kidney injury, and which was similar to our study in this respect (Ali, Khan et al. 2007).

The mortality rate among ICU patients requiring dialysis was very high, at 49%. This figure is higher than reports from the Finnish Acute Kidney Injury (FINNAKI) study, a recent multicentre trial looking at patients in Finnish ICUs, which reported a 90 day mortality rate of 33.7% (Nisula, Kaukonen et al. 2013). This may be due to the fact that

in our study we had a higher proportion of patients with stage 3 acute kidney injury, who comprised 41% of the overall patient mortality.

The strongest independent predictor of mortality on multivariate analysis in our study was mechanical ventilation (OR, p-value, 95% CI). This finding was similar to the finding in the multinational and multicentre study of acute renal failure in critically ill patients conducted by Uchino, Kellum et al. This study was undertaken before the introduction of the consensus definition of acute kidney injury and found mechanical ventilation to be one of the independent risk factors for in hospital mortality (Uchino, Kellum et al. 2005).

Another possible explanation for the finding that mechanical ventilation was an independent predictor of mortality in our patients is that there is evidence to suggest that deleterious organ cross-talk occurs between the kidneys and distant organs. This is due to cytokine related pathways (Feltz, Van Eyk et al. 2008). Additionally, there is evidence, from both animal and human studies, to suggest that primary acute lung injury itself may contribute to acute kidney injury (Grams, Rabb 2012). This was illustrated by findings from the first Acute Respiratory Distress Syndrome Network Trial conducted from 1996 to 1999. This study found that 24% of patients with acute respiratory distress syndrome developed acute kidney injury (defined as a serum creatinine level higher than $177\mu\text{mol/l}$) within the first four days of enrolment in the study (De Campos 2000, Grams, Rabb 2012).

Variables carrying a borderline significant association with mortality on multivariate analysis in our study were sepsis (OR 1.83, p-value 0.066, 95% CI 1.02-3.27), and time to dialysis (OR 1.93, p-value 0.080, 95% CI 0.93-4.03. This was consistent with previous studies that identified both as carrying mortality associations (Bagshaw, Uchino et al. 2007, Mehta, T PASCUAL et al. 2004).

Although our findings demonstrated an increase in 30 and 90 day mortality rates with increasing severity stage of acute kidney injury, it was not an independent predictor of 90 day mortality on univariate analysis. This may be because a large proportion of the patients had stage 3 acute kidney injury, which may have been a confounder in the ability to detect the effect of the stage of acute kidney injury on mortality in our patients. However, as previously discussed, other studies have shown a clear correlation between increasing mortality and acute kidney injury severity (Thakar, Christianson et al. 2009).

Renal recovery

The 80.5% rate of full renal recovery in our patients was lower than that reported in the Northern Scotland study by Ali et al, which reported full renal recovery rates of 92.5% (Ali, Khan et al. 2007). In addition, the percentage of patients with partial renal recovery (16.8%) is worrying in a country with limited access to renal replacement therapy. This is because such patients will require follow up and, at a later stage may require initiation of chronic dialysis. (Naicker 2009, KDIGO 2012).

A significant finding was that all of the patients going into end stage renal disease (no renal recovery) started off with an abnormal baseline serum creatinine. This finding of the acceleration of underlying chronic kidney disease to end stage renal disease after an episode of acute kidney injury is consistent with findings in other studies (Ishani, Xue et al. 2009, Venkatachalam, Griffin et al. 2010).

Only 53.1% of the patients who were alive at 90 days were available for a follow up serum creatinine. This was despite continued efforts to contact patients by telephone. As a result, some of the follow up serum creatinine results were obtained from laboratory records of patients returning for follow up or for admission under different departments.

We therefore compared the characteristics of the patients who had returned for follow up serum creatinine at or after 3 months to those who had not, in order to detect any differences between them that could affect our interpretation of the pattern of renal recovery in our study population. We found more mechanically ventilated patients among those returning (p-value 0.017). We also found that these patients were slightly older (p-value 0.049). Other comparisons incorporating data on demographics, management and sepsis found no differences between the two groups.

A large proportion of patients that did not exhibit full renal recovery was the 19-40 age group. Although this age group also had the highest rates of HIV infection (61.3%), (thus predisposing them to chronic kidney disease in the form of HIV associated

nephropathy), we found no correlation between HIV and renal recovery (p-value 0.383) in our study.

Timing of dialysis

One of the objectives of this study was to assess the effect of timing of dialysis on patient outcomes. Although the study was not adequately powered to make definitive conclusions about these effects, we found that there was a borderline increase in mortality risk with delayed chronological time to dialysis (OR 1.93, p-value 0.080, 95% CI 0.93-4.03).

As previously discussed, delayed chronological time to dialysis was found to be a better mortality indicator than BUN and serum creatinine levels in the BEST KIDNEY study, which discussed the potential confounders with the use of these biomarkers (Bagshaw, Uchino et al. 2007).

The available evidence therefore seems to suggest that earlier dialysis has better outcomes (Gibney, Bagshaw et al. 2008).

Study limitations

This was a prospective study of real time clinical practice, which employed retrospective analysis. As a result, the data obtained was dependant on that recorded by the clinician, and required patient data may have been missed due to clinician time limitations.

Many patients did not have a baseline serum creatinine level and, of those who did, the lowest reading over the last year was recorded as the baseline. Previous studies have used the ADQI recommendation of estimating the baseline serum creatinine level based on the Modification of Diet in Renal Disease (MDRD) study equation, which assumes a normal baseline GFR (Bellomo, Ronco et al. 2004). We elected not to use the MDRD equation in our study, instead deeming patients to have had acute kidney injury based on recovery of renal function, where a baseline serum creatinine level was missing.

This decision was based on evidence that the accuracy of the MDRD study equation has limitations (Bagshaw, Uchino et al. 2009). Evidence suggests that using the MDRD equation in estimating the baseline serum creatinine level (for purposes of determining a patient's RIFLE classification) is more useful if the baseline creatinine level is near normal. Furthermore, it has been concluded that the MDRD equation overestimates the incidence of acute kidney injury in those with chronic kidney disease (Bagshaw, Uchino et al. 2009).

Due to missing patient variables, we were not able to use physiological severity illness scoring methods such as the APACHE score. However, acute kidney injury stage was used as the main marker of patient illness, as it has been shown to correlate to mortality outcome (Thakar, Christianson et al. 2009). We also relied on a retrospective study of

medical ICU patient records carried out by Barrantes et al which found that acute kidney injury as defined by the AKIN criteria, was a better predictor of in-hospital mortality than the APACHE II score (Barrantes, Tian et al. 2008).

Another limitation in our study was the low proportion of patients returning for 3 month follow up. Nonetheless, we found that among the patients that did not return for follow up, fewer were mechanically ventilated and that they were younger. This could suggest that they were less severely ill than those returning for follow up, and that the results obtained can be expected to be a reasonable reflection of renal recovery in our patient population.

The last limitation of this study was that it was not funded. We were therefore not able to hire a dedicated research assistant to assist with data collection. This had an impact on our ability to adequately cross-check for missing data and therefore may have compromised the completeness of data.

Conclusion and Recommendations

This is the first study to look at the epidemiology, management and outcome of the full spectrum of acute kidney injury among patients referred to the Groote Schuur Hospital Renal Unit. Our study is unique among studies from the region in that we set out to follow up patients at 3 months in order to assess renal recovery and progression to chronic kidney disease. To our knowledge, other studies in the region have only focused on in-hospital outcomes.

Our study found that acute kidney injury carries a high mortality risk and that this risk is highest among mechanically ventilated patients. We also found that sepsis and delayed time to dialysis may be associated with a high mortality risk.

A significant proportion of patients with hospital acquired acute kidney injury had stage 3 acute kidney injury and sepsis. Based on this finding, we recommend that efforts be made to enable early detection and treatment of deteriorating patients. Such efforts could involve the use of an early warning scoring system that can be incorporated into patient observation charts. As previously discussed in this paper, a study of the use of this system in hospitals in the United Kingdom found that it enabled early detection of patients at risk of adverse outcome and prompt intervention.

A key finding in this paper was that basic bedside investigations and fluid balance chart records were missing in a significant number of patients. As these are essential in the assessment of patients with acute kidney injury, we recommend that efforts to improve

on this be made. This may need to involve hospital management as it relates to human resource capacity.

We also found that a significant number of patients did not have full renal recovery; a factor that contributes to the burden of chronic kidney disease in the Western Cape region. This reinforces the importance of a management plan that requires patient follow up at 3 months following an episode of acute kidney injury.

Lastly, we considered the impact of HIV as a risk factor when determining patient outcome. We found that while HIV is an important co-morbidity to consider in South Africa, it was not a predictor of mortality and renal recovery in the patients that we studied.

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UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Faculty of Health Sciences Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
e-mail: sumayah.ariefdien@uct.ac.za

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Dr T Dlamini
c/o Prof B Rayner
Renal Unit
E-13
NGSH

Dear Dr Dlamini

PROJECT TITLE: AN AUDIT OF ACUTE KIDNEY INJURY - A PROSPECTIVE STUDY OF THE EPIDEMIOLOGY, MANAGEMENT AND OUTCOME OF PATIENTS WITH ACUTE KIDNEY INJURY, OVER A 12 MONTH PERIOD AT GROOTE SCHUUR HOSPITAL, CAPE TOWN, SOUTH AFRICA (A TERTIARY LEVEL TEACHING HOSPITAL)

Thank you for addressing the issues raised by the committee.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above-mentioned study.

Approval is granted for one year till the 28 July 2013.

Please submit a progress form, using the standardised Annual Report Form (FHS016), if the study continues beyond the approval period. Please submit a Standard Closure form (FHS010) if the study is completed within the approval period.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

T. Sages
DP
PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

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Name & GSH Reference:

Date of birth:

M/F:

Date:

Hospital Admission- Date:

Referral Date:

Reason for referral:

Baseline Creatinine & Date:

Current Creatinine:

Past history (Medical/Surgical/Obs&Gynae):

Family Hx:

Medication/toxins/drug sensitivities/Allergies:

Habits:

Family Bloodlines:

Examination:

Urinary or the test - Y/N

BP	HR	RR	Temp	Sats	Ventilator/FiO2	Intraop dose	Vitals/sgluc
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General:

Derm./Musc-Skel/Endo:

RS:

CVS:

Abd/GUS:

Neuro:

ADG:

Fluid state (hypovolaemic/euvolaemic/hypervolaemic):

Urine Vol past: 6hrs:

24hrs:

<8hrs:

Fluid intake past 24 hours & Type (Enteral/ IV/ Medication/ Blood products):

INVESTIGATIONS - Baseline creatinine:

COMPLETE FLOW CHART OVERLEAF:

Urine dip	Urine M/cr.	Chest X-Ray	ECG	Renal US\$	Hep D	Hep C	HIV
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Assessment:

Plan (Dialysis - Y/N):

Renal Dialysis required - Y/N/Change:

Dialysis Modality	Dialysis mode	Blood pump speed	UF ² Y/N	Duration	Heparin Y/N/ml-dialy/dtrate	UF goal
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Plan continued:

Renal biopsy results

PATIENT	RENAL BIOPSY RESULT
1	ATN, GRANULOMAS – ZIEHL NEELSEN STAIN POSITIVE GRANULOMAS
2	HIVAN, GRANULOMAS
3	ASCENDING PYELONEPHRITIS
4	CRESCENTS, MESANGIOCAPILLARY GN
5	ATN, GRANULOMAS
6	LUPUS NEPHRITIS CLASS V, NECROTISING LESIONS, CRESCENTS
7	ACUTE POST INFECTIOUS GN
8	NECROTISING LESIONS, GRANULOMAS
9	ATN, INTERSTITIAL HIVAN
10	MESANGIOPROLIFERATIVE GN, ATN, GRANULOMAS
11	HIVAN, ACUTE INTERSTITIAL NEPHRITIS*
12	MESANGIOPROLIFERATIVE GN, ATN
13	MESANGIOCAPILLARY GN, CRESCENTS
14	MESANGIOCAPILLARY GN, CRESCENTS, LUPUS NEPHRITIS CLASS IV
15	MESANGIOCAPILLARY GN, CRESCENTS, ?LUPUS NEPHRITIS CLASS IV, ATN
16	MESANGIOCAPILLARY GN, ?LUPUS NEPHRITIS CLASS IV
17	ATN
18	NECROTISING LESIONS, IgA
19	ACUTE POST STREPTOCOCCAL GN/POST INFECTIOUS GN
20	ACUTE MESANGIOCAPILLARY GN, CRESCENTS, ACUTE INTERSTITIAL NEPHRITIS
21	ACUTE POST STREPTOCOCCAL GN/POST INFECTIOUS GN
22	EOSINOPHILS, GRANULOMAS
23	HIVAN
24	ATN, HIVAN
25	GRANULOMAS, ATN, INTERSTITIAL FIBROSIS
26	HYPERTENSION WITH CRENATION, ? ATN, INTERSTITIAL FIBROSIS
27	ATN, EXCLUDE LIGHT CHAIN DEPOSITION DISEASE

28	ACUTE POST STREPTOCOCCAL GN
29	HIVAN, MALIGNANT HYPERTENSION, ASCENDING PYELONEPHRITIS
30	MALIGNANT HYPERTENSION, ASCENDING PYELONEPHRITIS, INTERSTITIAL FIBROSIS
31	MEMBRANOUS GN, HIVAN – FOETAL VARIANT, HYPERTENSION
32	MALIGNANT HYPERTENSION
33	MESANGIOCAPILLARY GN, CRESCENTS, LUPUS NEPHRITIS CLASS IV
34	ACUTE POST INFECTIOUS GN, CRESCENTS
35	MESANGIOCAPILLARY GN
36	HIVAN, GRANULOMAS, ASCENDING PYELONEPHRITIS

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- ABOUT
- BOARD MEMBERS
- DONOR PROJECTS
- NEWS
- CONTACT
- Board Chairperson
- Office Manager
- Financial Administrator
- Office Secretary
- DONATE
- Terms and Conditions

You are here: Home > NEWS > Groote Schuur Fast Facts

Groote Schuur Fast Facts

Patient Activities 2011/2012 Financial Year

Inpatient Admissions	50 324
% Bed Occupancy	86%
Average Length of stay (days)	6
Operations	24 857
Deliveries	5 491
% Private Patients	12%
Outpatient Attendances (excluding service groups)	325 286
Total Number of Beds in Use - as at 1 May 2012	940

