A retrospective review of the profile and clinical course of patients requiring acute dialysis at Chris Hani Baragwanath Academic Hospital over a 2-year period

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A Research Report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfillment of the requirements for the degree
Of
Master of Medicine

Johannesburg, 2014

DECLARATION

I, Dr Mohammed Variava declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the Department of Internal Medicine at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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Dr Mohammed Variava MBBCh (Wits) FCP (SA)

DEDICATION

To my amazing wife, Firdous Variava, for her love, understanding, motivation and inspiration.

To my parents, Ishaak and Fatima Variava & Hassen and Nazma Sheik Ebrahim, for their support and instilling a passion for education.

ABSTRACT

Background

Acute kidney injury (AKI) is a condition with high rates of mortality and morbidity in the hospital setting. Various factors, such as social, political and ethical dilemmas are closely associated with scarce resources in the management of AKI in Africa. We therefore reviewed the demography, causes and outcomes of AKI at Chris Hani Baragwanath Academic Hospital (CHBAH).

Methods

A retrospective review of 324 patients with renal failure who were initiated on acute dialysis at the CHBAH over the periods of 1 July 2009 to 30 June 2011 was done.

Results

The mean age at presentation with AKI was 40±13 years. Males accounted for 57% whist 92% of the total cohort were Black. HIV positivity occurred in 26% of patients, whilst 4% and 2% of the cohort had Hepatitis B and C infection respectively. The leading causes for initiation of acute dialysis included decompensated chronic kidney disease (38.9%), acute tubular necrosis (ATN) (38.3%), HIV related kidney disease (13.6%), pregnancy-related kidney disease (7.4%), glomerulonephritis (7.4%) and malaria (5.7%). Acute tubular necrosis due to sepsis was the predominant cause of AKI in HIV positive patients. Decompensated chronic kidney disease was present in a large proportion of patients, suggesting that chronic co-morbid diseases such as hypertension and diabetes mellitus occurred in a large proportion of the general population. Medical referrals accounted for 78% of the patients presenting with AKI.

Renal recovery occurred in patients presenting with a lower average pre-dialysis blood urea level of 34±19 mmol/l, compared to higher levels seen in patients with poorer outcomes ($p < 0.0001$). Pregnancy- related kidney injury had the lowest average pre-dialysis blood urea levels of 20±6 mmol/l. The average pre-dialysis serum creatinine in patients with renal recovery was 804±467 µmol/l compared to those with poorer outcomes, that had average serum creatinine levels of greater than 1000 µmol/l at initiation of dialysis ($p < 0.0001$).

The overall renal recovery rate was 31%, with a mortality rate of 23%. Failure to regain renal function with subsequent chronic consequences occurred in 44.6% of patients, of which 23% were transferred to chronic renal replacement therapy and the remaining 21.6% of patients were transferred to Renal out patients department with cessation of acute dialysis.

HIV positive patients had a greater renal recovery rate (36% vs 26%); however they had a higher mortality rate compared to their HIV negative counterparts (34% vs 19%); ($p < 0.0001$). HIV positive patients with CD4 counts greater than 200 cells/µl had a 46% renal recovery rate compared to 30% in patients with CD4 counts less than 200 cells/µl ($p=0.1894$). Mortality with CD4 counts less than 200 cells/µl was 38% compared to 26% in patients with CD4 counts greater than 200 cells/µl ($p=0.1894$). Mortality rates were similar in HIV positive patients treated with antiretrovirals (ARVs) compared to those that were ARV-naive ($p =0.5857$).

Pregnancy-related kidney injury and malaria both had high rates of renal recovery, 92% and 79% respectively.

Discussion

The mean age of presentation of AKI were consistent with other studies in developing countries but was substantially lower than in developed countries such as the United Kingdom and Spain. The underlying aetiology of AKI at CHBAH resembles that of other developing nations with ATN, malaria and pregnancy-induced kidney injury being amongst the leading causes. Acute tubular necrosis still remains a common cause of AKI in South Africa as previously documented by Seedat et al. Malignancy and obstructive uropathy occurs at a much lower frequency compared to developed nations. The leading cause in HIV positive patients is ATN secondary to sepsis. Mortality occurred in 23% of the cohort, with HIV positive patients having a much higher mortality of 34%, concurring with a Johannesburg-based study by Vachiat et al.

Initiating dialysis at lower blood urea and serum creatinine levels in all patent groups had a much better outcome, including in HIV positive patients.

Conclusion

AKI remains a common presentation that frequently requires dialysis, a scarce resource in an already overburdened health system, with a high mortality rate. HIV positive patients had a higher mortality rate compared to HIV negative patients; however a higher renal recovery rate was observed in this group. CD4 count and ARV status had no statistical significant effect on outcomes, probably due to the small sample size.

ACKNOWLEDGEMENTS

Professor S Naicker, a brilliant person, leader, mentor, academic and my co supervisor, whose encouragement and commitment to this project was unparalleled. Every step in this journey was carefully guided by Professor Naicker. For this, I will always be grateful to have been given the opportunity of working with someone of this magnitude in the Nephrology world.

Dr M. Mashabane, Head of the Renal Unit at CHBAH, my co supervisor. I am eternally grateful for the help and support that you have provided for me during these last few years.

Dr A Bentley, who assisted me with ideas, reviews and statistics.

Dr Firdous Variava, my dear and amazing wife, who assisted me with data collection and statistics.

Mr Living Shivambo, a patient at CHBAH who assisted me with data collection, unfortunately demised prior to the completion of this project.

Lastly and most importantly, the patients at CHBAH, without whom this project would not be possible.

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ABBREVIATIONS

ACE	Angiotensin converting enzyme
ADQI	Acute Dialysis Quality Initiative
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
ARF	Acute renal failure
ARV	Antiretroviral
ATN	Acute tubular necrosis
CHBAH	Chris Hani Baragwanath Academic Hospital
ESRD	End stage renal disease
FSGS	Focal segmental glomeruosclerosis
GN	Glomerulonephritis
HAART	Highly active antiretrovirals
HD	Haemodialysis
HELLP	Acronym for Haemolysis, Elevated Liver enzymes, Low Platelets
HIV	Human immunodeficiency virus
HIVAN	Human immunodeficiency virus associated nephropathy
HIVICK	Human immunodeficiency virus immune complex kidney disease
HUS	Haemolytic uraemic syndrome
ICU	Intensive care unit
NRTI	Nucleoside reverse transcriptase inhibitors
NSAIDS	Non steroidal anti inflammatory drugs
PD	Peritoneal dialysis
RIFLE	Acronym for Risk, Injury, Failure, Loss and End stage disease
ROPD	Renal outpatient department
RRT	Renal replacement therapy
SIRS	Systemic inflammatory response syndrome
SLE	Systemic lupus erthyematosis
TDF	Tenofovir
TIN	Tubulo interstitial nephritis
TTP	Thrombotic thrombocytopaenic purpura

CHAPTER 1. LITERATURE REVIEW

1.1 Historical Perspective

The evidence of kidney disease historically dates back to the time of the ancient Egyptians (1). Egyptians were one of the first civilizations to begin collecting and recording medical knowledge due to their constant desire for eternal life. The preservation of their knowledge in medical papyri reflects the great capacity of Egyptians for treating symptoms, but lacks the abstract thought that was to come with the more rational Greek medical era. Multiple references are made to symptoms such as haematuria, urinary retention, frequency and infection in ancient Egyptian records (1). These accounts have been matched by the Greeks, Romans and Byzantines who also correlated clinical syndromes with certain diseases that affect the kidney (2). These include pyuria, pain and fever indicative of diseases such as pyelonephritis, kidney abscess formation as well as the relationship between systemic sepsis and oliguria. These ancient records can all be extrapolated in modern times as the major aspects of acute kidney injury (AKI).

Hippocrates, one of the most influential people of all times, has made huge contributions to medical knowledge (3). Hippocratic medicine laid the foundation of the development of clinical nephrology and he is considered the “Father of Nephrology” (4). Despite the huge advances in modern renal medicine, Hippocratic practices, emphasizing clinical observations, prognostication and ethical influences can never be overlooked and are part and parcel of not only medicine but plays a large role within the nephrology world (5).

During the renaissance period many medical advances were made; however, the association of oedema with renal failure was only identified in the late 18th century (6). Proteinuria was discovered in this period facilitating the birth of the modern approach to kidney disease (7). Bright provided the first complete clinical description of the various forms of acute and chronic glomerulonephritis (GN) with accompanying macroscopic changes in 1827 (8, 9). His contribution to the nephrology world has proven to be enormous. The amount of new knowledge acquired during the 20th century has been tremendous, and covers all the mechanisms of urine formation, the role of sodium retention in oedematous states, the physiology and pathophysiology of the renin-angiotensin-aldosterone system, nephrotic and nephritic syndromes, new methods of investigation, progress in histology and immunology, the discovery of many tubular syndromes, the introduction of antibiotics and antihypertensive drugs and the development of dialysis. These advancements in nephrology have led us to the modern age of renal medicine that encompasses a vast array of pathology and disease processes.

1.2 Definitions of acute kidney injury

Acute kidney injury is characterized by a decline in kidney function that can manifest over a few hours to days. This leads to an increase in nitrogenous waste products within the bloodstream, resulting in the symptoms that may become apparent during the illness (10).

The lack of a standard definition of AKI has impacted on the progress of clinical and basic research in this field (11). A review of 26 studies involving post operative renal failure in the mid nineties showed that no two studies used the same definition when defining acute renal

failure (ARF) (12). This highlights the inconsistencies within the medical fraternity and AKI. Until recently, no consensus existed on how best to define, characterize, and study AKI.

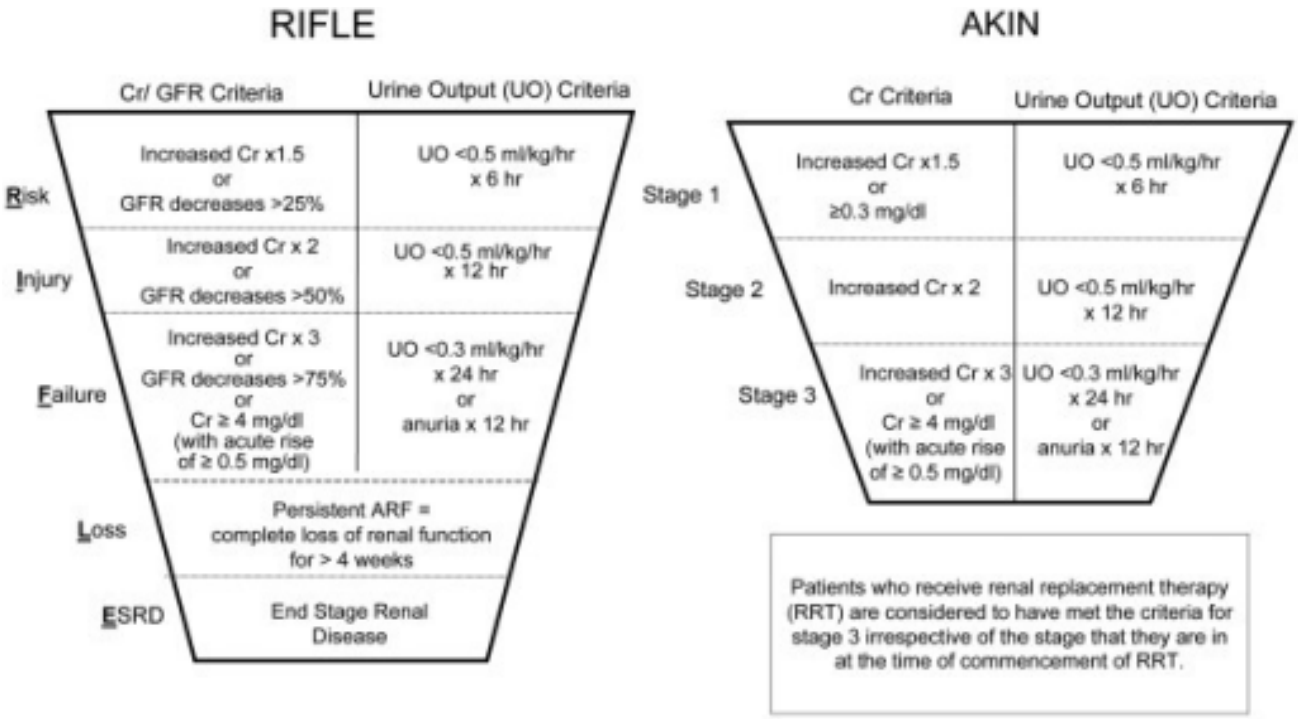
The Acute Dialysis Quality Initiative (ADQI) group of experts developed and published the RIFLE criteria in 2004 (13, 14). The RIFLE classification has become the most widely used and adopted method of standardization of AKI with almost 30 studies using this definition. These criteria, which make up the acronym 'RIFLE', classify renal dysfunction according to the degree of impairment present: risk (R), injury (I), failure (F), sustained loss (L) and end-stage kidney disease (E) (15). This new classification system has transformed acute kidney disease. This disease entity can now be viewed as a spectrum of kidney disease and hence the emergence of the term, AKI rather than ARF (16).

The RIFLE scoring system has been reviewed and studied in many centres around the world, particularly in critically ill patients. The results have been consistent in various studies. In a large heterogeneous cohort of critically ill patients, the increase in severity of RIFLE categories is associated with an increase in mortality (17). The RIFLE classification (Figure 1) is a simple, readily available clinical tool to classify AKI in different population groups (18).

In 2007, The Acute Kidney Injury Network (AKIN) made a few modifications to the RIFLE criteria resulting in the birth of the AKIN criteria (Figure 1). The first 3 stages are kept with a few minor changes. These are called AKIN Stage 1, AKIN Stage 2 and AKIN Stage 3. The loss and end stage kidney disease categories of the RIFLE classification do not feature in the AKIN classification.

The two classifications, seen in Figure 1, can detect AKI with both high sensitivity specificity and describe severity levels that predict the prognosis of affected individuals, particularly those in intensive care (15). Both the RIFLE and AKIN classification utilize an increase in serum creatinine level from baseline as well as a decrease in urine output (19). These surrogate markers of renal impairment usually manifest much later after kidney injury, however are readily available in clinical practice (20).

Figure 1: RIFLE and AKIN Classification



Reference: www.ccforum.com (Accessed from the internet in February 2013) (21)

Direct comparison of the 2 classifications show similar sensitivity and ability to predict outcomes in ill patients (20).

The KDIGO guideline (22), published in 2012, defines AKI based on any of the following:

- Increase in serum creatinine of greater than 26.5µmol/l within 48 hours; or
- Increase in serum creatinine of greater than 1.5 times the baseline over 48 hours; or
- Urine output of less than 0.5ml/kg/hr for 6 hours.

The stages of AKI based on the KDIGO guidelines are presented in Table 1. These stages have prognostic value and resemble the AKIN classification.

Table1: Stages of AKI

Stage	Cr. Criteria	Urine Output Criteria
1	SCr X 1.5-1.9 times baseline or a rise of ≥ 26.5µmol/l	UO < 0.5ml/kg/hr x 6hrs
2	SCr X 2-2.9 times baseline	UO < 0.5ml/kg/hr x 12 hrs
3	SCr X 3 times baseline or a rise ≥ 353.6 µmol/l or Initiation of renal replacement therapy or a decrease in eGFR of < 35ml/min/1.73m	UO < 0.3ml/kg/hr x 24 hrs or Anuria ≥hrs

Reference: *Khwaja A. KDIGO Clinical Practice Guidelines for Acute Kidney Injury. Nephron Clinical practice. 2012;120(4):179-84. (22)*

1.3 Biomarkers and acute kidney injury

Acute kidney injury is a serious abnormality that results in severe metabolic, electrolyte and fluid abnormalities in the body. These effects occur later in the presentation of AKI and serum biomarkers such as serum creatinine increase later in the disease (23), thus emergence of biomarkers for the earlier detection of AKI are currently being explored. At present, serum creatinine is the only readily available biomarker in clinical practice and is the gold standard.

Biomarkers can be divided into 4 main categories that include functional markers, up-regulated proteins, low molecular weight proteins and enzymes (24).

Table 2: Biomarkers in AKI

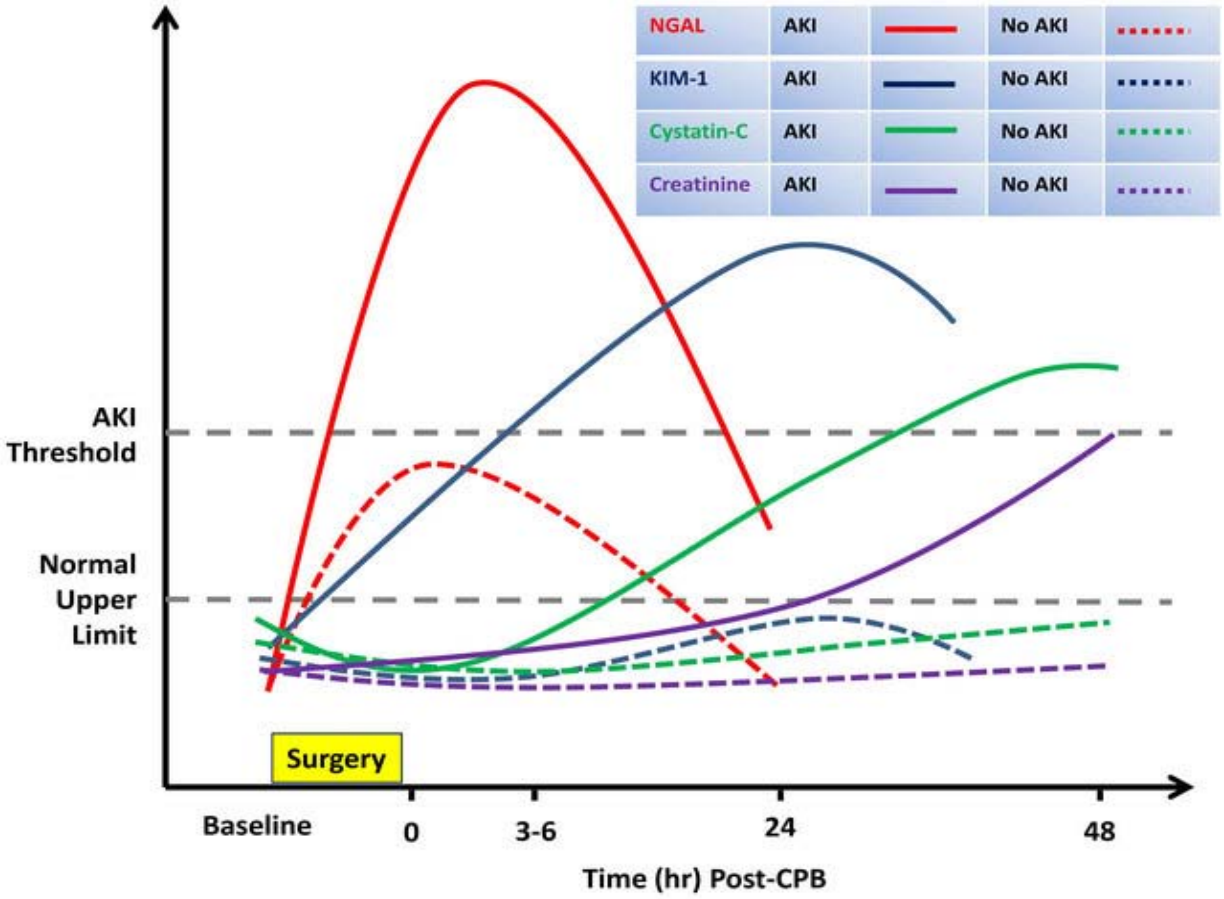
Functional markers	Up regulated proteins	Low molecular weight proteins	Tubular enzymes
Serum creatinine	Nuetrophil gelatinase-associated lipocalin (NGAL)	Urine cystatin C	Alpha-glutathione s-transferase (α-GST)
Plasma/serum cystatin C	Kidney injury molecule-1 (KIM-1)		Pi-glutathione s-transferase (π-GST)
	Liver fatty acid binding protein(L-FABP)		Gammaglutanyl transpeptidase (GGT)
	Interleukin-18 (IL-18)		Alkaline phosphatase (ALP)
			N-acetyl-β-D-glucosaminidase(NAG)

de Gues H.R.H et al – Biomarkers for the prediction of acute kidney injury: a narrative review on the current status and future challenges. Clin Kidney J (2012) 5:102-108 (24)

The biomarkers represented in Table 2 are directly related to the pathophysiology of kidney injury at various cellular levels. The majority of these markers are expensive but importantly are only beginning to be explored as a research tool within the nephrology world. These markers rise very early in the course of AKI and have the potential for earlier detection of

AKI as seen in Figure 2. The biomarkers depicted in Figure 2 clearly show the peaked levels of concentration of the biomarkers occur much earlier after an insult compared to serum creatinine levels.

Figure 2: Comparison of biomarkers concentrations related to time



Reference: Zheng CM et al. Biomarkers in acute kidney injury. OJ Neph. 2013;3(1):51-60. (25)

Biomarkers have been studied in various centres around the world with varying results obtained (24). The majority of the studies evaluated the various biomarkers independently of each other. Results currently indicate that biomarkers have a potential role to play in the earlier diagnosis of AKI but larger studies need to be performed in order to utilize these markers in clinical practice. They are also reported to have prognostic implications. Clinical

appraisal of a patient using serum creatinine remains the cornerstone of diagnosis at present (26).

1.4 Epidemiology of acute kidney injury

The incidence of AKI around the world is not well known (27). Studies done in the United States of America have shown incidences of 23.8 per 1000 with an 11% yearly increase from 1992 to 2001(28). Similar results were obtained from a Spanish review published in 1996, showing an increase in the rate of AKI in recent times, with a significant contribution from iatrogenic causes as well as the development of AKI in the peri-operative period (29).

Acute kidney injury has been reported to occur in 1% of hospital admissions (30). Approximately 2-5% (31) are affected by kidney injury during hospitalisation and as many as 15% of patients develop AKI after certain types of surgery such as cardiopulmonary bypass surgery (23).

The pattern of AKI in emerging countries is changing, albeit at a slower pace compared to that in developed countries. A study done in Northern India showed a vast difference in the rates of AKI between two different time frames. There was a decline from 23% to 10% in patients with AKI caused by diarrhoeal illness from the periods 1965-1974 and 1981-1986 respectively. A similar decline was also noted with sepsis-related AKI, however the overall causes and actual frequencies are different from the developed countries with regards to community-acquired AKI (32). A second study compiled by the same group in India assessed spectrums of hospital-acquired AKI in developing countries and found that results

were similar to that of technologically advanced countries, although the pattern of community acquired AKI is vastly different (33).

Martin Luther King once commentated "Of all the forms of inequality, injustice in health is the most shocking and the most inhumane." There has been a clear discrepancy between the epidemiology between developed and developing world (34). Socio-economic discrepancies are one of the major contributors to the disparities between these two worlds. Together with cultural practices, infective pathology as well as availability of resources, these have resulted in the current epidemiological pattern of AKI that is seen in the developing world.

The differences between developed and developing countires are caused by various factors. Financial implications are probably one of the most important aspects. Money has always driven the world and the medicine is no exception. More money translates to more research, better drug development, easy access to these medications and health care, all of which enables the developed countries to move forward. With financial backing, richer nations have an overall better healthcare infrastructure and resources and improved access to healthcare. Resources such as dialysis and better equipment are pivotal in improving mortality from renal disease. These challenges have been one of the largest factors in the high levels of morbidity and mortality in Africa.

The social aspect of a nation is often neglected when assessing disease. The socio-political scene of any nation is essentially the driving force of the country and dictates the above

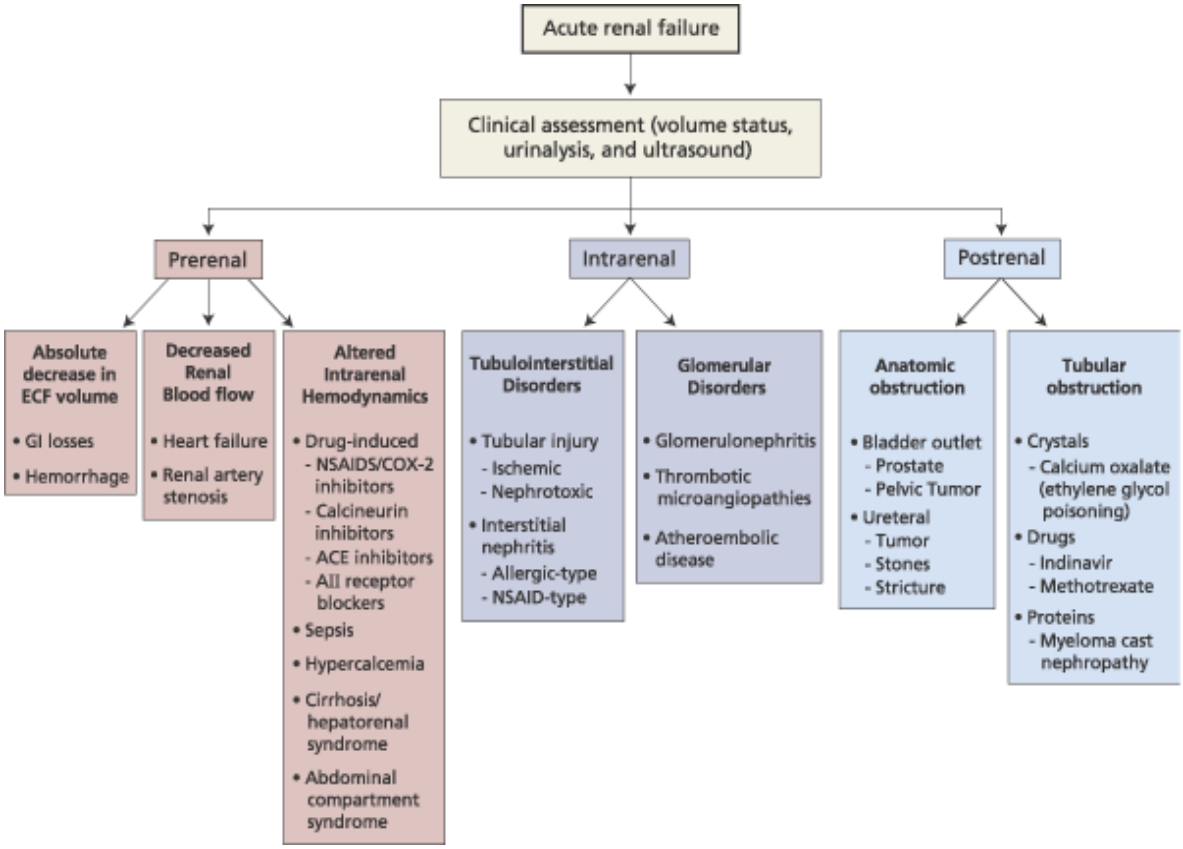
factors directly. Poor sanitation, housing, overcrowding and poverty are just a few examples that have been shown to have major effects on disease epidemics in developing nations. Many outbreaks such as diarrhoeal illness secondary to poor sanitation, have been seen in developing nations almost exclusively, with high mortality rates (35).

Acute kidney injury in the developed world is often seen in the geriatric population. Functional changes that occur in the ageing kidney lead to a reduced glomerular filtration rate, lower renal blood flow and impaired renal auto-regulation (36). AKI is often iatrogenic and multifactorial, commonly superimposed on pre-existing renal dysfunction, and resulting from exposure to nephrotoxins such as radio contrast agents, aminoglycosides, NSAIDs, ACE inhibitors and diuretics.

1.5 Causes of acute kidney injury

Acute kidney injury comprises of a diverse spectrum of disease entities. It can be assessed as a syndrome or constellation of features whereby a decline in kidney function occurs, ultimately resulting in severe morbidity and mortality, if not recognized and treated adequately.

Figure 3: Causes of acute kidney injury



www.pharmaworld.pk.cws3.com (Accessed from the internet in May 2013) (37)

Various mechanisms are involved in the pathophysiology of AKI. These insults render the functional unit of the kidney, the nephron, with reduced capabilities of fulfilling its functions. These functions include urine production, fluid balance, maintenance of electrolyte balance, excretion of toxic substances and ability to accomplish the important endocrine functions of the kidney. All of these functions are interrupted substantially, leading to the signs and symptoms that develop in AKI (10).

The causes of AKI in Africa have a different pattern when compared to Europe, Australia or the United States of America. Infective causes, both HIV-related sepsis and non-HIV related

diseases are amongst the major contributors to AKI. Naicker et al, reviewed the major causes of AKI in Africa as seen in Table 3. Infective causes such as malaria, diarrhoeal illness, HIV, obstetrical causes and toxins were the leading causes of AKI in Africa and similar patterns were seen in various regions of Africa (34).

Table 3. Causes of AKI in Africa

Country	Causes of AKI
North Africa	
Algeria	Toxins, trauma/surgery, urologic
Egypt	Surgical, toxins, obstructive
Morocco	Haemodynamics, sepsis, obstructive
West Africa	
Cameroon	Malaria, obstetric, toxins
Cote d'Ivore	Malaria, HV, toxin
Nigeria	Sepsis, obstetric, toxin
Senegal	Obstetric, malaria, herbal toxins
Democratic Republic of Congo	Infections (especially malaria), hypovolaemia, toxin
East Africa	
Kenya	Infection, obstetric, surgical
Burundi	Malaria, dehydration (HIV, diarrhoea)
Rwanda	Infections, trauma, toxins
Ethiopia	Malaria, surgical, acute glomerulonephritis
Eritrea	Infection
Sudan	Infection, toxins
Southern Africa	
South Africa	Infections (including HIV), toxins, pregnancy
Mozambique	Malaria, dehydration, obstetric
Zimbabwe	Prerenal (HIV), malaria, obstetric
Zambia	Malaria, obstetric
Malawi	Diarrhoeal disease, malaria, sepsis

Reference: Naicker S et al. Epidemiology of acute kidney injury in Africa. Seminars in Nephrology. 2008;30(9):2051-8 (34)

In South Africa, the causes of AKI have also transformed over the last few decades. An epidemiological study done in Durban in 1978 showed that the leading cause of AKI was

herbal toxin ingestion (38). A review approximately 10 years later showed that sepsis replaced toxin ingestion as the leading cause in South Africa (39). More recently, HIV infection has been reported as a major contributor of AKI (40). Causes such as malaria, pregnancy induced kidney injury, glomerulonephritis (GN) and post surgical related AKI are still occurring albeit at a lower frequency than previously noted

1.5.1 Acute tubular necrosis and acute kidney injury

Acute tubular necrosis (ATN) and AKI are often mistakenly used interchangeably. ATN is a cause of AKI that is common in the hospitalized patient. In one study, ATN accounted for 38% of cases with AKI for hospitalized, non intensive care unit (ICU) admissions (41) and rose to 76% of cases with ATN as their cause of renal failure when in ICU (41). ATN can be either ischaemic or toxin-related. Sustained pre-renal states are the most common factor for ischaemic ATN (41, 42) in both community-acquired and hospital-acquired kidney injury. Thus, fluid status and correction of these states early in management is pivotal in managing these patients and preventing significant morbidity and mortality.

Sepsis is an extremely important and common cause for the development of ATN and ultimately AKI. In the ICU setting, sepsis is the leading cause of AKI in up to 51% of cases as reported in a French prospective study (43). Septicaemia can result from community-acquired infections such as pneumonia, urinary tract infections, osteomyelitis, infective endocarditis as well as infections at other sites. It can also result from more virulent hospital acquired infections due to a vast array of organisms that include bacterial, fungal and viral infections.

The mechanisms and events resulting in renal dysfunction in sepsis are poorly understood. The systemic inflammatory response syndrome (SIRS) (44) which results in systemic hypotension with activation of vasoconstrictor hormones as well as the induction of nitric acid synthase and nitric oxide, which are potent vasodilators. All of which further compounds the poor perfusion state of the kidney and worsens the injury. Further release of cytokines, reactive oxygen species, and the activation of neutrophils by endotoxins all contribute to renal injury at the cellular level (45, 46).

Other important considerations for the development of ATN include drugs and toxins. These are most often iatrogenic, as seen with contrast-induced nephropathy (47), drugs such as aminoglycosides, NSAIDs and ACE inhibitors in certain conditions (48, 49). Medical doctors need to be aware of these interactions and monitor their patients closely for these side effects particularly in the geriatric population.

Other toxins are self inflicted and these include recreational drugs (50), herbal and traditional medications. The mechanisms for these effects on the kidney may either be direct nephrotoxicity or indirectly related (51). Herbal intoxication and traditional medications have gained favour particularly in the African (52) and Asian (53) continent. Many of the constituents are not laboratory tested and their safety is unknown. These agents have been linked predominantly with renal and liver toxicity. Traditional medication is a common practice in South Africa (54) and hence an important cause of AKI. This form of AKI is common and often difficult to treat, due to its rapid progression within the kidney as well as

its predilection for other vital organ systems. Early intervention is pivotal and often patients need to be admitted to ICU due to other comorbid dysfunction related to the toxin ingestion.

1.5.2 Tubulo-interstitial nephritis and acute kidney injury

Tubulo-interstitial nephritis (TIN) is a form of inflammation affecting the interstitium of the kidneys surrounding the tubules. This disease can be either acute, meaning it occurs suddenly, or chronic, meaning it is ongoing and eventually ends in chronic kidney failure. The major cause of TIN is often drug-related. A study in Boston in 2004 showed that 92% of TIN was caused by drugs.. This study also assessed the use of corticosteroids in the treatment of TIN and found no statistical benefit in its use (55).

Most of the antibiotics including commonly prescribed ciprofloxicillin, penicillin, cephalosporins and vancomycin are associated with the development of TIN. Other commonly used drugs such as diuretics, NSAIDS, proton pump inhibitors, phenytoin, allupurinol and antivirals have also been noted as causative agents. The diagnosis may be confirmed by renal biopsy, however simple auxiliary investigations such as a urinary eosinophil count can suggest TIN but has poor sensitivity (56).

1.5.3. HIV and acute kidney injury

HIV infection has become one of the major pandemics in the world. The Sub-Saharan region has been enormously impacted upon and carries the highest burden of this disease, including financial implications (57). South African medicine has seen a major transformation over the last 3 decades and the nephrology world is no exception.

AKI is commonly observed in patients infected with the HIV (58). The underlying causes of AKI in HIV are often multifactorial (59). These may range from the direct effect of HIV, opportunistic infections and medication related factors. Table 4 illustrates the classification of AKI in HIV positive patients (60).

Table 4: Classification of AKI in HIV

Pre-renal Causes
Hypovolaemia: diarrhoea, nausea/vomiting, decreased oral intake
Effective hypovolaemia: hypotension, sepsis, liver disease, hypoalbuminaemia(nephrotic syndrome, proteinuria, malnutrition)
Intrinsic Renal Injury
Acute tubular necrosis
Ischaemic: hypovolaemia, shock, sepsis, cardiopulmonary compromise
Nephrotoxic: medications, radio contrast
Rhabdomyolysis
Parenchymal infection (mycobacterial, fungal, viral)
Interstitial nephritis
Haemolytic uraemic syndrome
Glomerular disease: HIVAN, glomerulonephritis
Post Renal Causes
Intra-renal tubular obstruction: crystaluria from medications, tumour lysis syndrome
Ureter or bladder obstruction: nephrolithiaisis, lymphadenopathy/tumour, fungus ball, blood clots, neurogenic bladder

*Reference: Kalim et al –Acute kidney injury in HIV-infected patients. Seminars in Nephrology.2008;28(6):556-62 (*60*).*

A French study published in 1999 biopsied HIV positive patients with renal failure, reported several different causes of AKI. These ranged from ATN, haemolytic uraemic syndrome, HIVAN and drug related nephrotoxicity (61).

One of the most common renal entities caused by HIV is HIV-associated nephropathy (HIVAN) (62). This condition is characterized by severe proteinuria, rapid progression to renal insufficiency, and a morphologic pattern of collapsing focal segmental glomerulosclerosis (FSGS) on renal biopsy (63-65). Its progression to end stage renal disease is well known and hence makes up an increasingly large population of patients needing renal replacement therapy (RRT), posing a serious burden with regards to resources (57) . Although HIVAN is the predominant glomerular lesion in HIV infection, other reported glomerular lesions include HIV-immune complex kidney disease (HIVICK), IgA nephropathy, cryoglobulinaemia, amyloidosis, and a lupus-like immune complex glomelorulopathy (66, 67). While these are chronic glomerular conditions, they frequently present acutely with renal failure and need to be considered when evaluating patients with AKI. In the pre-antiretroviral therapy era, HIVAN was characterized by rapid progression to end stage renal disease (ESRD) and death. Highly active antiretroviral therapy (HAART) has changed the natural course of this disease, highlighting the importance of prompt diagnosis and appropriate care (68).

A study done at CHBAH, in 2006 showed that up to 27% of HIV positive patients with renal disease had HIVAN. A further 21% were diagnosed with HIVICK (69). Another study done

in Kwazulu Natal during a similar timeframe also confirmed the high prevalence of HIVAN in South Africa (70).

Treatment of HIVAN has also changed in the last 15 years. In one study, the rate of progression from the initial presentation to ESRD was 2.5 months in the pre-HAART era(71). The introduction of HAART has significantly slowed down this progression (71) (72). Other treatment options include early institution of ACE- inhibitors (73, 74) as well as corticosteroids (75-77) which have been shown to be beneficial in certain groups.

The most common cause of acute renal insufficiency is prerenal azotaemia from depletion of the intravascular volume. This can be a result of both “true” and “effective” depletion. Other common causes include direct damage to the renal tubules from both nephrotoxic medications and prolonged ischaemic processes that occur frequently in hospitalised patients. Injury to the tubulo-interstitium of the kidney may also result from allergic reactions to medications prescribed to patients. Deposition of crystals in the tubules, and rarely in the glomerular capillaries, will cause AKI in the setting of tumour lysis syndrome or during therapy with medications that result in crystal nephropathy. Finally, obstruction of the urinary system may cause post renal azotaemia in patients infected with HIV (60).

With the advent of HAART, increased rates of kidney injury from drug related effects have been reported. Common nephrotoxic effects associated with HAART include crystal-induced obstruction secondary to the use of protease inhibitors (mainly indinavir and

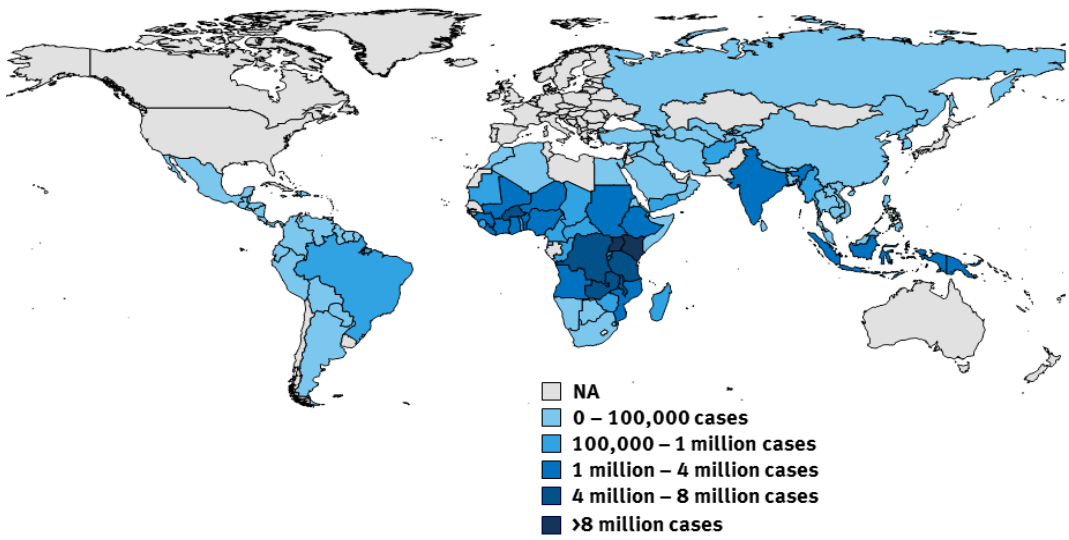
atazanavir), and proximal tubular damage related to the nucleoside reverse transcriptase inhibitors (NRTI), namely tenofovir (TDF). Acute kidney injury can occur following TDF-induced tubular dysfunction or as a result of severe mitochondrial dysfunction and lactic acidosis induced by this NRTI (78). Withdrawal of the drug leads to improvement of parameters (79), however support may be needed with RRT during the recovery phase. Importantly, the benefits of HAART outweigh the risks and hence HAART should not be avoided on this account but rather caution and close monitoring of renal parameters should be observed.

HIV has increased the need for dialysis both in the acute as well as chronic setting (80). A study done in Cape Town showed that patients with HIV and AKI secondary to ATN and CD4 count of more than 200 have a good survival outcome (81). Risk factors for poorer outcome in HIV positive patients include co-existing Hepatitis C infection (82), black race, low CD 4 counts and pre existing chronic kidney disease (83). The Johannesburg study by Vachiat et al showed that outcomes in HIV positive and HIV negative patients were similar when offered dialysis and supportive care (40).

1.5.4 Malaria and acute kidney injury

Malaria remains one of the most common diseases in the world, with a high burden in Africa. Four species of malaria affect humans, however, malaria infection caused by *Plasmodium malariae* or *Plasmodium falciparum* is recognized as an important cause of AKI and severe metabolic acidosis in complicated malaria (84).

Figure 4: Reported cases of Malaria in 2011



Reference: Kaiser Family Foundation. World Malaria Report 2012.www.GlobalHealthFacts.org, ***(85)***

The increasing incidence of malarial AKI represents a serious challenge in both South Africa and around the world. Most of South Africa, apart from areas in Kwazulu Natal, Limpopo and Mpumalanga are malaria free zones. The disease, however, still occurs in large numbers due to factors such as migrant labour, immigration from neighbouring states and the entity of taxi malaria. There has been a changing trend recently not only in the clinical manifestations, but also in the pattern of complications in malaria. Over a decade

ago, cerebral malaria was the predominant manifestation of severe malaria, whereas today the combination of jaundice and renal failure are more common (86).

Acute kidney injury is seen most commonly in *Plasmodium falciparum* infection (87), however other malarial species can also induce renal injury. Since the precise mechanism of malarial AKI is not well known, several hypotheses have been made which include mechanical obstruction by infected erythrocytes, immune mediated glomerular and tubular pathology, fluid loss due to multiple mechanisms and alterations in the renal microcirculation (87).

Malaria often has a deadly course in patients who are not treated early. Acute kidney injury requiring dialysis remains a common presentation in malaria (88) and frequently results in a poor outcome. In a study done in India in 2001, 92 % of patients with malaria and AKI went on to require dialysis (89). A recent review in Saudi Arabia in 2010, showed that 78% of patients with malaria and AKI required dialysis (90). These high rates are in accordance with other studies and show the large number of patients infected with malaria resulting in renal failure that requires dialysis.

1.5.5 Pregnancy and acute kidney injury

Acute kidney injury poses a serious challenge when occurring in pregnancy. Acute kidney injury in pregnancy can be induced by any of the disorders leading to renal failure in the general population, such as ATN due to infection, glomerulonephritis related to lupus, or drug toxicity. There are, however, pregnancy complications characteristic of each trimester that can result in renal failure (91).

In the first trimester, AKI occurs commonly due to hypovolaemic states secondary to the hyperemesis gravidarum or ATN secondary to septic abortions. Later in pregnancy, microangiopathic haemolytic diseases such as preeclampsia together with the HELLP syndrome and TTP-HUS are seen with drastic consequences (92, 93). These disease entities have specific characteristics and need to be diagnosed timeously and appropriate interventions instituted.

Pregnancy-related AKI is a rare entity in developed countries but still occurs commonly in the developing world. A study done in 2013 in India showed that 11,5% of all AKI were pregnancy related. Sepsis, preeclampsia and haemorrhage were the major causes with a maternal mortality rate of 15% and a foetal mortality rate of 41.7% (94).

A South African study published in 1995 showed that up to 16% of pregnancy related AKI required dialysis. The leading causes of AKI were preeclampsia and septic abortions (95). A prospective study carried out in an ICU setting, showed that as many as 25.8% of patients with eclampsia developed AKI and had a substantial mortality rate of 36.1% (96).

Pregnancy-related AKI remains a serious problem with high maternal and foetal mortality rates.

1.5.6 Malignancy and acute kidney injury

Certain malignancies such as multiple myeloma, genitourinary cancers and hepatocellular carcinomas have an increased risk and frequency of developing AKI (97). Multiple myeloma specifically causes various forms of kidney disease, however the majority of the consequences lead to chronic kidney disease (98). Acute kidney injury in multiple myeloma is often a result from factors such as dehydration, sepsis, hypercalcaemia, hyperuricaemia and chemotherapy related. The spectrum of renal lesions, typically chronic related, include cast nephropathy, amyloidosis (AL subtype), monoclonal immunoglobulin deposition disease and, less frequently, cryoglobulinaemic GN and proliferative GN (99).

Tumour lysis syndrome is a constellation of biochemical and clinical abnormalities resulting from rapid and massive tumour cell death. It often occurs at the onset of treatment in particularly in tumours of high bulk burden. It is frequently associated with hyperuricaemia, hyperkalaemia, hyperphosphataemia, and secondary hypocalcaemia that may lead to serious clinical complications, including AKI and cardiac arrest (100). This effect is often noted in haematological malignancies but can occur with solid tumors particularly after chemotherapy.

Malignancies are also associated with GN. One of the theories for the cause is that a viral agent is responsible for both the cancer and the GN (101). The most common GN associated with malignancies, particularly haematological malignancies, is membranous GN. One study showed that 10.7% of patients with a biopsy proven membranous GN had a concurrent malignancy (102). The rate of developing AKI requiring dialysis is less frequent and is associated with dehydration, sepsis, hypercalcaemia and drug toxicity.

Chemotherapeutic drugs in the treatment of cancer are often nephrotoxic and an important cause of AKI in malignancy as many are nephrotoxic (103) . Lastly, the bulk of the tumour itself can result in obstructive uropathy at the various anatomical levels of the genitourinary tract as commonly seen in cervical cancer, bladder and renal carcinoma.

1.5.7 Other causes of acute kidney injury

Other causes of AKI include crush syndrome with rhabdomyolysis, acute GN specifically poststreptoccal GN, autoimmune diseases such as systemic lupus erythematosis (SLE) and scleroderma with acute renal crisis, microangiopathic haemolytic anaemias and obstructive uropathy from any cause.

1.6. Treatment of acute kidney injury

1.6.1 Supportive treatment

The treatment modalities for AKI are largely supportive measures especially in the early stage of the disease. Supportive measures include the following:

- Airway, breathing and circulation need to be firstly addressed and the patient adequately optimized
- Blood pressure monitoring and appropriate intervention taken, particularly if the patient is severely hypotensive, the use of inotropes or fluids can be considered depending on the underlying cause of the decrease in blood pressure
- The appropriate use of blood products
- Assessing and addressing electrolyte derangements, with careful consideration for potassium, sodium, calcium and phosphate as these are often deranged with a high mortality if not adequately corrected
- Maintaining acid/base balance
- Close monitoring of urine output and hydration status of the patient

A careful history, examination and directed investigations need to be done in order to ascertain the underlying cause of theAKI. Once the cause is identified, the main goal of treatment is to treat the underlying cause of AKI. For example; if sepsis from a bacterial organism is the culprit, adequate antibiotic therapy needs to be started in conjunction with supportive measures.

1.6.2 Dialysis

Acute kidney injury poses a serious and often difficult complication of any underlying disease process. With cessation or decline in kidney function, nitrogenous waste accumulates and results in the severe symptoms seen in patients with kidney dysfunction. These include; uraemic bleeding, pericarditis, metabolic acidosis, encephalopathy, pulmonary oedema and life threatening electrolyte disturbances. In order to counteract these effects, dialysis needs to be instituted urgently.

The concept of dialysis was born in the early 20th century by Dr. J Abel from John Hopkins Medical School in Baltimore. It was not until 1946, where a Dutchman, Dr. Willem Kolff achieved the breakthrough whereby a patient with AKI was dialysed and survived for the first time. Advances were then quickly made in this field and by 1960, the first long term chronic kidney patient began dialysis with success. Further improvements have been made and now various dialysis options are available with improved functionality and electrolyte control.

The two main types of dialysis include peritoneal dialysis (PD) and haemodialysis (HD). Various factors ranging from both patient related and disease related are taken into consideration in deciding which modality to institute.

Peritoneal dialysis can be an option in resource poor settings and is often used; it is less frequently utilised in AKI in South Africa at present. Peritoneal dialysis utilization has markedly declined for various reasons especially in countries with the resources to have all options at their disposal. The use of PD is precluded in some circumstances, such as after major abdominal surgery or severe trauma. Another drawback with PD is the inadequate

fluid volume control during dialysis. There are also concerns that the presence of dialysate in the peritoneal cavity may cause diaphragmatic splinting and result in higher ventilatory pressures in mechanically ventilated patients (104).

A prospective study of 204 patients with AKI on PD was assessed in Brazil and showed that PD was effective in correction of metabolic acidosis and fluid control in a selected group of patients but had a high rate of mortality in the elderly and in severe sepsis (105). A systematic review in 2013 assessed the use of PD compared to HD and found no difference in outcomes between the two modalities (106); however more research is clearly needed to assess this option. Peritoneal dialysis is an established form of chronic RRT in our hospital and remains a favoured choice for many ambulatory patients due to the various advantages that it can offer. Peritonitis rates have been shown to be similar to that of developed countries as seen in a study conducted at CHBAH. (107)

Haemodialysis remains the most commonly used modality in our setting at present. It allows for better and more accurate control and titration of electrolytes and fluid removal. The morbidity of HD is largely related to the insertion of the central venous catheter, occurence of deep vein thrombosis, cardiovascular instability and sepsis (108). Haemodialysis can be given intermittently or continuously. In ICU settings and in particular in patients with severe haemodynamic instability, continuous veno-venohaemo diafiltration is the preferred option.

1.7 Timing of dialysis

The time for initiating dialysis remains controversial. Pre-dialysis blood urea and serum creatinine levels are not used in isolation. The pre-dialysis blood urea levels were assessed in a multicentre study. This study showed that initiating dialysis at high urea levels had a higher 60 day mortality rate (109). Urea levels are however affected by factors independent of kidney function. These include protein intake, catabolic state, gastrointestinal bleeding, pregnancy, chronic alcohol abuse and the use of corticosteroids (110).

Serum creatinine levels closely relate to the current definition of AKI as it forms the basis of both the RIFLE and AKIN criteria (20). The pre-dialysis creatinine level is not routinely used as a measure for initiating dialysis on its own but rather in conjunction with other variables.
The pre-dialysis serum creatinine was evaluated in a Cape Town study, which found a better outcome in HIV positive patients with AKI that were dialysed at lower pre-dialysis serum creatinine levels (81). Creatinine, however, is also influenced independently of the kidney and hence has limitations regarding its use in isolation, particularly in AKI and sepsis (111).

1.8 Outcomes of acute kidney injury

The major outcomes in AKI are renal recovery, death or need for chronic RRT. According to the RIFLE criteria, a diagnosis of chronic kidney disease may be made 3 months after the initial acute insult (16). Acute kidney injury is an independent poor prognostic marker for long term outcomes inclusive of mortality and development of CKD (112).

Renal recovery in AKI is defined as normalization of renal function within 3 months after the initial insult; however the majority of studies addressing renal recovery includes only critically ill patients that require acute dialysis and consider renal recovery as dialysis independency at hospital discharge (113). Higher rates of renal recovery have been documented in developed countries with rates of 56%, 61.8% and 68% respectively for renal recovery in patients with AKI (114-116). Renal recovery rates have been substantially lower in developing countries, as seen in India, where one study had a renal recovery rate of 43% (117). In South Africa, rates of renal recovery have been as low as 33.3% in HIV positive patients (81).

The need for chronic RRT is often a result of AKI. In one study, 15% of patients required chronic RRT after an acute insult (117). This is consistent with other literature which has rates of approximately 12.5% of patients with AKI requiring chronic RRT (118).

Mortality rates of AKI vary from study to study. AKI independently increases mortality rates and has been shown to increase mortality by 5.5 fold (119). The mortality of AKI differs between ICU and non-ICU settings. Audits done in non-ICU patients both in developed and developing countries have mortality rates of between 24-46% (29, 117, 120). Patients that require dialysis within the ICU setting almost invariably have multiple other co-morbidities including respiratory, cardiac and liver failure. Renal failure requiring dialysis within an ICU setting has been shown to be a specific and independent risk factor for poorer prognosis. (121). A prospective multicentre study done in Austria analyzed over 17000 medical,

surgical and obstetric patients admitted to ICUs over a 2-year period. Close to 900 (5.3%) of these patients had renal failure requiring dialysis and this group showed a statistically significant higher hospital mortality rate and poorer outcomes compared to those patients with no renal dysfunction. Studies in Australia have shown mortality rates of as much as 46.8 % (122) and 49.2% (123) amongst ICU patients requiring dialysis, compared to patients not requiring dialysis.

1.9 Justification for study

Limited data is available from South African hospitals over the last few years. The aim of this study is to audit the epidemiology of AKI that required dialysis. The causes of AKI in our population will be analysed as well as the outcomes of AKI at CHBAH.

1.10 Aims and Objectives

1.10.1 Aims

The aim of the study is to compile a profile and outcomes of all patients that were dialysed acutely at CHBAH over a two year period.

1.10.2 Objectives

The objectives include the following

- to determine the demography
- to determine the disease profile, including aetiology of primary renal disease and chronic co morbidities. Co-infection with HIV, Hepatitis B and Hepatitis C will be reviewed.
-to establish the pre dialysis blood urea and serum creatinine and relation to outcomes
-to assess the aetiology of AKI and relation to outcomes
-to compare the demography and outcomes in HIV positive and HIV negative patients with AKI requiring dialysis.

CHAPTER 2: METHODS

2.1 Study Design

A single centre retrospective review of patients that were acutely dialysed by the Nephrology Unit of CHBAH during the period of 1 July 2009 to 30 June 2011.

Patients were selected from the electronic records of the CHBAH Renal Unit known as “BART”, which is an acronym for “Baragwanath Active Renal Tracking” system. A list was obtained from the electronic records and matched with records of patients that were acutely dialysed during this timeframe.

2.1.1 Inclusion criteria

The inclusion criteria included all patients who were:

- greater than 14 years of age
- presented to CHBAH between 1 July 2009 to 30 June 2011
- dialysed from the wards, Medical, Obstetrical and Burns High Care Units

2.1.2 Exclusion criteria

Exclusion criteria included all patients who:

- were solely initiated on dialysis in the ICU
- had incomplete records

2.2 Ethics

The University of the Witwatersrand Ethics Committee granted ethics approval unconditionally in May 2012 (clearance certificate M120412 – Appendix A).

Confidentiality was maintained throughout the data collection process. A separate coding system known only to the primary investigator was used with the last 6 digits of the hospital number together with the first letter of the patient surname.

2.3 Data collection and analysis

The data collected, included the following (see Appendix B):

-Age

-Sex

-Race

-HIV status ± CD4 count ±ARV status

-Hepatitis B and C serology

-Pre-dialysis blood urea

-Pre-dialysis serum creatinine

-Cause of kidney injury

-Chronic co-morbidities (if any)

-Outcomes

Causes of kidney injury were diagnosed based on clinical, biochemical, sonographical as well as biopsy in some cases and documented on the BART system.

The chronic comorbidities included hypertension, diabetes mellitus, malignancy and other. Hypertension and diabetes were defined in accordance with the South African Hypertension Guidelines 2011 and the SEMDSA Diabetic Guidelines 2012 .

A computer program known as REDCap was used to capture and enter the data. REDCap is a tool that is Witwatersrand University-approved and users need to be registered with a Witwatersrand University staff or student card. This effective tool allows the researcher to capture data on a web designed data collection sheet that can be accessed via mobile devices such as a smartphone or tablet. This ensures a paperless data collection process. The REDCap service is a secure network whereby only the user with a secure username and password obtains access. This also allows for a backup to be made on a cloud server. The data collection sheet was electronically designed on REDCap and data was then successfully captured. See Appendix A for data collection sheet.

Majority of the data, including blood results, was obtained directly from the BART system however outstanding blood results such as HIV, Hepatitis B, C and pre-dialysis blood urea and serum creatinine were obtained from the NHLS blood tracking system using the patients' hospital numbers. The demographical data were obtained and placed on REDCap. The causes of the kidney injury were documented in the electronic records on the BART system. This was usually entered by the registrar/medical officer at the time of the initial consultation but would be invariably checked by a senior nephrologist. This helped to limit the misdiagnoses that may occur during the capturing done on the BART system. Once the REDCap database was completed, verification of data was done using tools readily available within the REDCap software. The data was then exported from REDCap into Microsoft Excel.

All descriptive statistics such as means, medians, frequencies, percentages as well as standard deviations and interquartile ranges were obtained from the Microsoft Excel spreadsheet. Graphs such as pie charts, frequency distribution tables and contingency tables were drawn from Microsoft Excel. The remaining outcomes that needed to be assessed were done with the help of Dr. A Bentley and Graph Pad. Statistical tools such as Chi-square, Fisher exact, ANOVA and Tukey-Kramer Multiple comparison tests were used.

Statistical significance was measured at the 5% level (p value of<0.05) for statistical significance.

2.4 Definitions of outcomes measured

The outcomes measured in this review were as follows:

- **Renal recovery**: Normalisation of renal function and independence of dialysis.
- **Transfer to chronic renal replacement therapy (RRT):** after initiation of dialysis, there is failure of full recovery and hence the need for transfer to the chronic programme for continuation of dialysis. The form of dialysis could be haemodialysis or peritoneal dialysis. The type of renal replacement therapy was not assessed.
- **Transfer to renal outpatients (ROPD)**: The cessation of dialysis after it was noted that the patient was a poor candidate for continuation of dialysis, or does not fulfill criteria for acceptance for chronic renal replacement therapy. This group also comprises those patients that did not regain full renal function but dialysis was not continued for various reasons that were not reviewed.

- **Death**: The patient was initiated on dialysis and demised
- **Loss to follow up**: Unknown outcome/loss to follow up
- **Poorer Outcomes**: defined as those patients that fail to regain kidney function and include the “transfer to chronic RRT’, “transfer to ROPD’ and “death” groups.

CHAPTER 3: RESULTS

3.1 All Patients

3.1.1 Demography and clinical data

The two-year audit comprised of all patients that were acutely dialysed at CHBAH from 1 July 2009 to 30 June 2011. A total of 340 patients were reviewed but only 324 were analysed. The remaining 16 patients were excluded, as minimal records regarding their diagnosis and demographic data were obtainable.

Table 5: Demography of patients that underwent acute dialysis

Number	324
Age (in years) [mean±SD]	40±13
Gender - Males	184(57%)
- Females	140(43%)
Race – Black	299(92.3%)
- Coloured	12(3.7%)
- White	8(2.5%)
- Indian	5(1.5%)

The demographics of all 324 patients are presented in Table 5. The mean age was 40 ± 13 years; 184 patients (57%) of the cohort were male; 299 patients (92.3%) comprised of Black race, followed by Whites (2.5%), Coloureds (3.7%) and Indians (1.5%) as depicted in Figure 5 and 6.

Figure 5:Race of patients on acute dialysis (N=324)

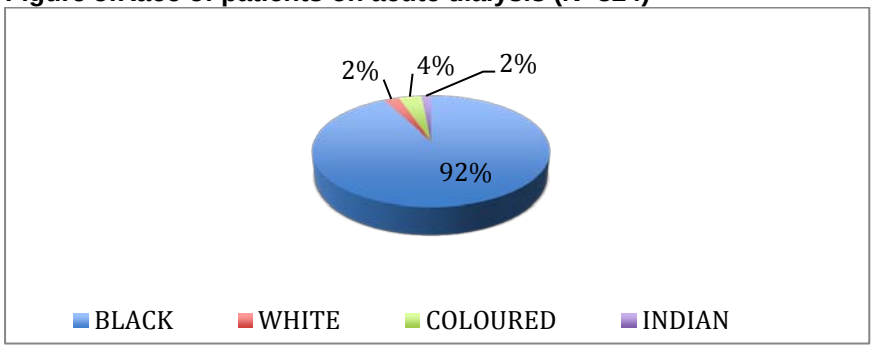
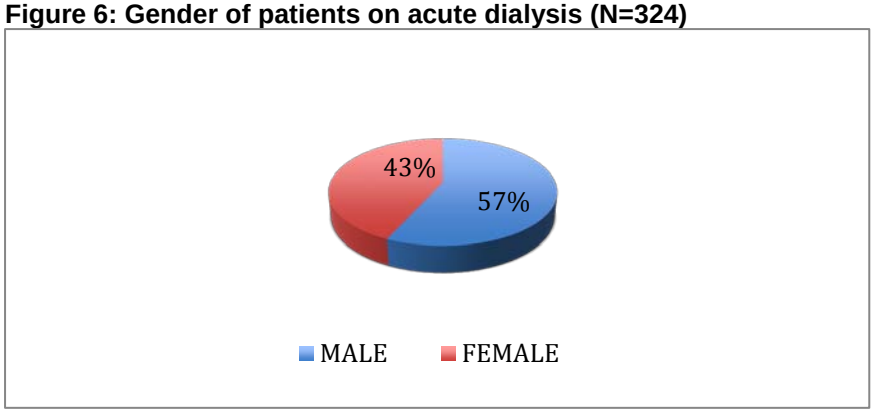
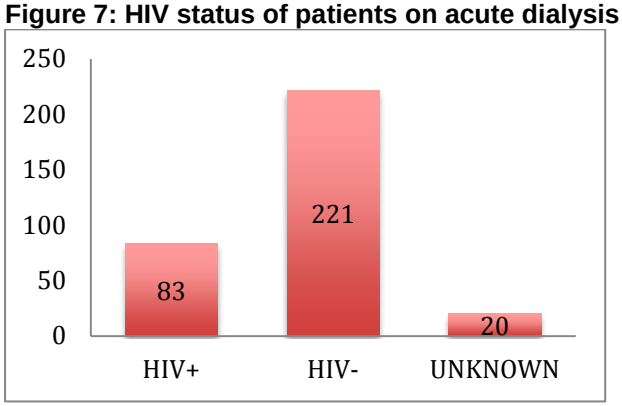


Figure 6: Gender of patients on acute dialysis (N=324)



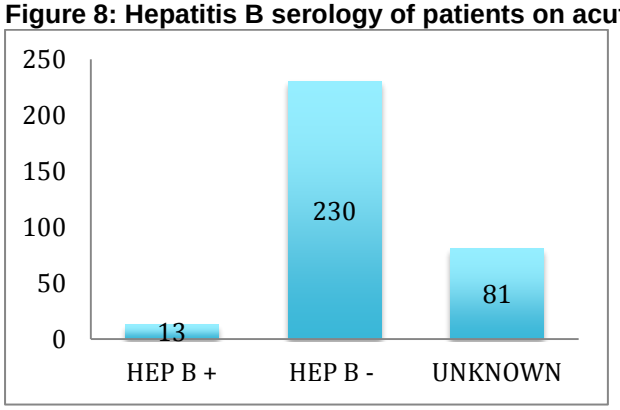
3.1.2 HIV, Hepatitis B and Hepatitis C status

Figure 7: HIV status of patients on acute dialysis



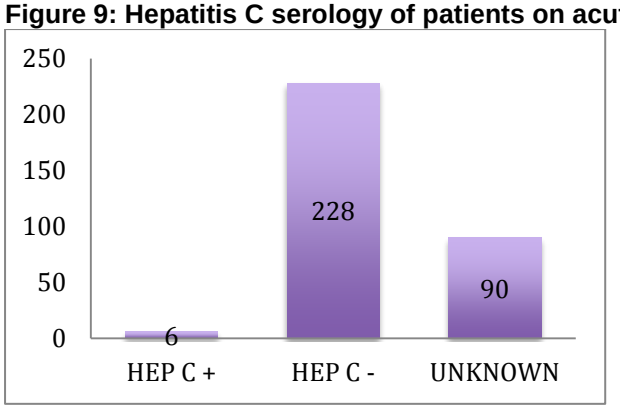
The HIV status of patients undergoing acute dialysis was analyzed in the cohort and presented in Figure 7. HIV positivity accounted for 83 patients (26%); in 20 patients (6%), the HIV status was unknown.

Figure 8: Hepatitis B serology of patients on acute dialysis



Hepatitis B serology is presented in Figure 8; 13 patients (4%) were Hepatitis B positive and 230 patients (71%) had negative Hepatitis B serology. A quarter of the cohort had unknown Hepatitis B status. Hepatitis B co-infection with HIV occurred in 3 of the 83 patients (3.6%) .

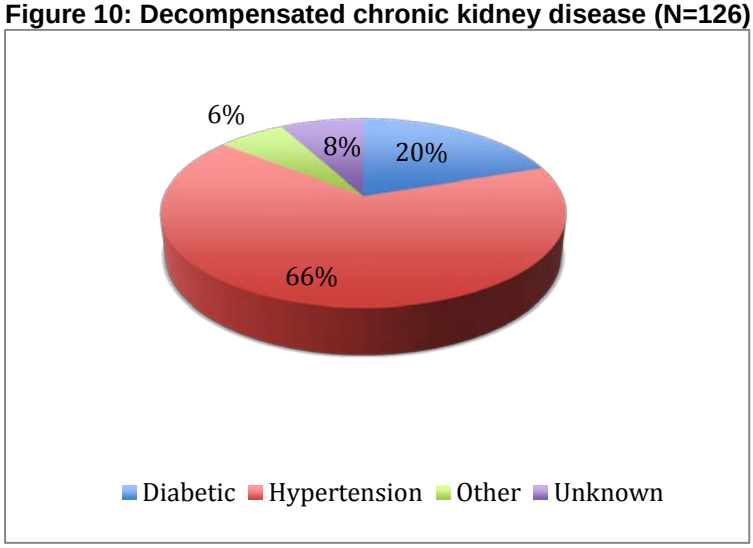
Figure 9: Hepatitis C serology of patients on acute dialysis



Six patients (2%) were found to be Hepatitis C positive (Figure 9). The majority of the patients were Hepatitis C negative (70%) however 28% of the cohort had an unknown Hepatitis C status. Co infection of Hepatitis C and HIV occurred in 1 patient (1.2%)

3.1.3 Decompensated Chronic Kidney Disease

Figure 10: Decompensated chronic kidney disease (N=126)



A large proportion of the patients had evidence of underlying chronic kidney disease and subsequently developed an acute on chronic deterioration of their renal function, resulting in the institution of acute dialysis. This group comprised of 126 patients (39%) of the cohort. Hypertension accounted for 66% of these patients, whilst diabetes mellitus was noted in 20% of the patients. At the time of institution of dialysis, 75 out of the 83 (90%) hypertensive patients were receiving treatment for hypertension. Sixteen (19%) of the hypertensive patients were hypertensive for more than 5 years.

Diabetes occurred in 25 patients. The types of diabetes were not recorded. Majority of diabetic patients were on treatment, (24 of the 25,96%), of which 12 (48%) were on treatment for more than 5 years. Eleven patients (9%) had both diabetes and hypertension.

The “other” group comprised of the following; Primary oxaluria (1 patient), Polycystic kidney disease (3 patients), dilated cardiomyopathy (2 patients) and chronic liver disease (1 patient)

3.1.4 Discipline of referral

Referral from the medical wards accounted for 254 patients (78%). The surgical wards and obstetrics wards accounted for 38 patients (12.5%) and 26 patients (8%) respectively. Six patients had an unknown ward of referral.

3.1.5 Causes of kidney injury

Figure 11: Causes of kidney injury

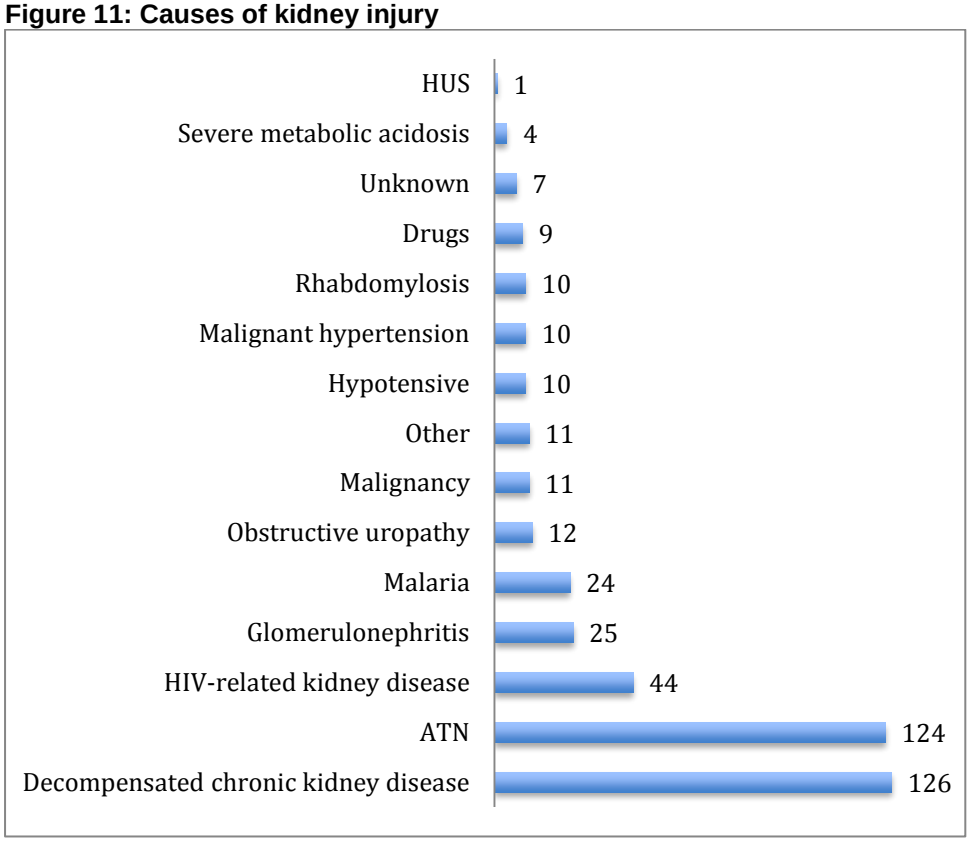


Table 6: Causes of ATN

Causes	Number
Sepsis	106
Toxin/Herbal	10
Pancreatitis	5
Contrast induced	3

Figure 11 depicts the causes of kidney injury in the 324 patients that were reviewed. Patients may have had more than one cause for the AKI.

Decompensated chronic kidney disease accounted for 126 patients (38.9%). ATN occurred in 124 patients (38.3%). The underlying causes of ATN are presented in Table 5. Sepsis, the second leading cause of renal failure requiring dialysis accounted for 106 (32.4%) of these patients, whilst herbal intoxication occurred in 10 patients. This group of patients were known to have taken a herbal/traditional medication that resulted in the insult. Pancreatitis with associated kidney damage occurred in 5 patients, with 3 patients having ATN secondary to contrast induced nephropathy.

HIV related kidney disease affected 44 patients (13.6%). 7 of these patients (16%) had a kidney biopsy done that showed HIV associated nephropathy. The remaining 84% were diagnosed with HIV related kidney disease based on HIV status, sonar features of hyperechoic ± enlarged kidney sizes, presence of proteinuria and clinical features of proteinuria and renal dysfunction. Other causes of AKI in HIV positive patients are tabulated in Table 10, with most HIV positive patients having more than one cause for the AKI.

Glomerular disease occurred in 24 patients (7.4%). These included both primary glomerolunephritis (G)N (10 patients) and secondary GN (14 patients). The primary GN was diagnosed on biopsy in 8 out of the 10 patients: Membraneous nephropathy (2 patients), cresenteric GN (2 patients), Membroproliferative GN (2 patients) and Focal segmental glomerulosclerosis (2 patients). The remaining 2 patients had a diagnosis of Primary GN noted on the system but details of the biopsies were not found in records. All patients with secondary GN were noted to have SLE.

Pregnancy-related kidney injury accounted for 24 patients (7.4%) that underwent acute dialysis. 19 patients (5.9%) were dialysed for acute kidney injury secondary to Falciparum malaria.

Obstructive uropathy accounted for 12 patients (3.7%) and malignancy, with associated kidney injury accounted for 11 patients (3.4%). The types of malignancies are presented in Table 7.

Table 7: Type of malignancies

Malignancy	Number
Non Hodgkins lymphoma	3
Multiple myeloma	2
Acute myeloid leukemia	1
Prostate cancer	2
Primary brain tumour	1
Renal cell carcinoma	2

Malignant hypertension, rhabdomyolysis and hypotensive states accounted for 10 patients each (3.1%). The hypotensive states included patients with cardiomyopathies, pulmonary embolus and valvular heart disease.

3.2 HIV infection and acute kidney injury

3.2.1 Demography and clinical data of HIV positive patients

Table 8: Demography and clinical data for HIV positive patients

Number	83
Gender – Male [n(%)]	41(49%)
- Female [n(%)]	42(51%)
Age (years)	39±11
CD4 count (cells/µl) [mean±IQR]	153(4-621)
Hepatitis B Positive [n(%)]	3 (3.6%)
Hepatitis C Positive [n(%)]	1(1.2%)
On ARVS [n(%)]	16 (19%)
Not on ARVS [n(%)]	51 (62%)
Unknown ARV status [n(%)]	16 (19%)
Pre dialysis blood urea level (mmol/l) [mean±SD]	43±21
Pre-dialysis serum creatinine (µmol/l) [mean±SD]	1053±581

HIV positivity accounted for 26% of patients presenting for acute dialysis. The average age of these patients was 39 ± 11 years; male to female ratio was approximately 1:1(Table 8).

Co-infection with both Hepatitis B and C occurred infrequently; however >35% of patients had unknown Hepatitis B and C serology.

The median CD4 count was 153 cells/µl (IQR 4 to 621 cells/µl). The median CD4 count of patients that were on ARVs was 240 cells/µl (IQR 106-621 cells/µl). The CD4 counts of the 51 patients not on ARVs were much lower, with a median of 83 cells/µl (IQR 4-572 cells/µl (Table 9),

Table 9: Median CD4 counts related to ARV status

	On ARVs (N=16)	Not on ARVs (N=51)
CD4 ± IQR (cells/µl)	240 (106-621)	83 (4-572)

16 patients (19%) were on ARVs at time of presentation, with 51 patients (62%) not on any treatment.

The average pre-dialysis blood urea and serum creatinine was 43±21 mmol/l and 1053±581 µmol/l respectively.

3.2.2 Causes of kidney injury in HIV positive patients

Table 10: Causes of kidney injury in HIV positive and HIV negative patients

	HIV Positive (N=83)	HIV Negative (N=221)
Decompensated chronic kidney disease	7	116
ATN	53	63
HIV related kidney disease	44	0
Glomerulonephritis*	2	21
Pregnancy	7	16
Malaria	13	5
Obstructive Uropathy	0	12
Malignancy	4	6
Other	4	7
Rhabdomylosis	1	5
Malignant hypertension	0	10
Hypotension	3	6
Drugs	4	5
Unknown	0	6
Severe Metabolic acidosis	0	3
HUS	1	0

* Primary GN accounted for 10 patients and secondary GN occurred in 14 patients

The disease spectrum of HIV and its impact on the causes of kidney injury resulting in the need of acute dialysis is shown in Table 10. All causes in both the HIV positive group and negative group are noted, however the HIV unknown group was not analysed. Primary glomerulonephritis, obstructive uropathy, contrast induced nephropathy and malignant hypertension occurred only in the HIV negative group.

Table 11: Top 5 causes of kidney injury in HIV positive patients

ATN	53
HIV related kidney disease	44
Malaria	13
Pregnancy	7
Decompensated kidney disease	7

The major cause of AKI in HIV positive patients is ATN, occurring in 64%, compared to HIV negative patients with only 29% being affected with ATN (Table 10 and 11). Patients may have had more than one cause for the AKI.

Malaria was the third most common cause of AKI amongst HIV positive individuals. 16% of HIV positive patients that were acutely dialysed had malaria.

Pregnancy-related kidney injury had similar frequencies in the two groups whilst there was a marked difference in the decompensated chronic kidney disease group. HIV positive patients only accounted for 8% compared to the HIV negative group with greater than 50% of patients with decompensated chronic kidney disease.

3.3 Demography and clinical data of patients with malaria

Table 12: Demography and clinical data of patients with malaria

Number	19
Gender – Male	17 (89%)
- Female	2 (11%)
Age (years)	39±12
HIV positive	13 (68%)
Pre-dialysis blood urea (mmol/l)	41±12
Pre-dialysis serum creatinine (µmol/l)	848±428

Nineteen patients (6%) requiring acute dialysis at CHBAH had Falciparum malaria. Males accounted for 89% (Table 12). The mean age was 39 ±12 years.

Majority of patients (68%) were co-infected with HIV. The average pre-dialysis blood urea was 41 mmol/l and the pre-dialysis serum creatinine was 848 µmol/l.

3.4 Demography and clinical data in pregnancy-related kidney injury

Table 13: Demography and clinical data of patients with pregnancy-related kidney injury

Number	24
Age (years)	28±7
HIV positive	7 (29%)
Pre-dialysis blood urea (mmol/l)	19±7
Pre-dialysis serum creatinine (µmol/l)	499±112

Pregnancy-related kidney injury accounted for 24 patients (7%) of the cohort. The mean age was 28±7 years. HIV positivity occurred in 29% of pregnant females (Table 13).

The pre-dialysis blood urea and pre-dialysis serum creatinine was 19±7 mmol/l and 499±112 µmol/l respectively.

The underlying cause of the pregnancy-related kidney injury is illustrated in Table 14.

Table 14: Causes of pregnancy-related kidney injury

Pregnancy related condition	Number
Pre-eclampsia/HELLP Syndrome	18
Eclampsia	2
Abruptio placentae	3
Post partum haemorhage	1

3.5 Outcomes

The outcomes assessed in this study group include the following:

- Renal recovery
- Transfer to chronic renal replacement therapy
- Transfer to Renal Outpatient Department
- Death
- Loss to follow up

3.5.1 Pre dialysis blood urea and outcomes

The pre-dialysis blood urea recorded was the last documented blood urea prior to commencement of dialysis. The mean was calculated and compared to each outcome.

Table 15: Pre-dialysis blood urea (mmol/l) in all patients

	Renal recovery	Transfer to chronic RRT	Transfer to ROPD	Death	Loss to follow up
ALL Patients*(N=324)	34±19	49±20	51±22	45±23	24±10
HIV +(N=83)	35±22	30±24	49±17	48±21	
HIV- (N=221)	34±18	50±19	53±24	44±23	27±6
Malaria (N=19)	39±25				
Pregnancy (N=24)	20±6				

*p value <0.0001

The mean pre–dialysis blood urea for all patients are presented for each outcome in Table 15. Pregnancy-related kidney injury had the lowest pre-dialysis blood urea level of 20 mmol/l compared to all patients with a blood urea of 34mmol/l. Lower pre-dialysis blood urea levels were observed in the renal recovery for all patient categories compared to

higher levels seen in the other outcomes that included transfer to chronic RRT, transfer to ROPD and Death. (p value <0.0001). ANOVA test was used.

Initiating dialysis at higher blood urea levels was associated with a poorer outcome in all patients (P<0.0001)

3.5.2 Pre-dialysis serum creatinine levels and outcomes

The pre-dialysis serum creatinine levels of each group were compared to outcomes as depicted in Table 16.

Table 16: Pre-dialysis serum creatinine levels (µmol/l) for all patients

	Renal recovery	Transfer to chronic RRT	Transfer to ROPD	Death	Loss to follow up
ALL Patients *(N=324)	804±467	1602±732	1335±634	1108±700	801±376
HIV +(N=83)	805±422	1010±794	1424±704	1046±490	
HIV- (N=221)	811±495	1627±725	1316±605	1188±824	867±380
Malaria (N=19)	831±403				
Pregnancy (N=24)	501±116				

*P value<0.001

The renal recovery group had a similar pre-dialysis serum creatinine of between 804-831 µmol/l for all patients except for the pregnancy induced kidney injury group. This group had much lower serum creatinines with an average of 501 µmol/l. There was statistical significance for renal recovery at lower pre-dialysis serum creatinine levels compared to the other outcomes (p value <0.0001).

3.5.3 Causes of acute kidney injury and outcomes

Table 17: Outcomes in all patients (N=324)

Outcome	Number
Renal Recovery	98 (31%)
Transfer to chronic RRT	75 (23%)
Transfer to ROPD	70 (21.6%)
Death	76 (23%)
Loss to follow up	5(1.4%)

The outcomes of all 324 patients analyzed are illustrated in Table 17. 98 (31%) patients had renal recovery; 23 % of patients were transferred to chronic RRT and offered chronic dialysis; 21.6% of patients were transferred to renal outpatients with cessation of their dialysis; 76 patients (23%) had demised.

Table 18: Outcomes of the leading causes of kidney injury

	Renal Recovery	Transfer to chronic RRT	Transfer to ROPD	Death	Loss to follow up
Decompensated CKD(N=126)	2(1.5%)	66(52%)	37(30%)	19(15%)	2(1.5%)
ATN (N=124)	39(31.5%)	4(3.2%)	27(21.8%)	52(41.9%)	2(1.6%)
HIV related kidney disease(N=44)	5 (11%)	2(5%)	18(41%)	19(43%)	0(0%)
Glomerulonephritis(N=24)	2(8.3%)	7(29.2%)	6(25%)	8(33.3%)	0(0%)
Pregnancy (N=24)	22(92%)	0(0%)	1(4%)	0(0%)	1(4%)
Malaria(N=19)	15(79%)	0(0%)	3(16%)	1(5%)	0(0%)
Obstructive Uropathy (N=12)	2(17%)	2(9.5%)	7(58%)	2(9.5%)	0(0%)

The outcomes of the leading causes of AKI in all patients are illustrated in Table 18. The decompensated CKD group had over 50% of patients transferred to the chronic RRT and continuation of dialysis; 15% of this group demised. 41.9% of the ATN group patients

demised, with 31.5% obtaining renal recovery. 11% of patients with HIV related kidney disease had renal recovery whilst 43% demised.

The glomerular disease group had 8.3% recovery, with one third of this group demising and 29.2% were placed on the chronic renal replacement program. The highest rate of renal recovery was the pregnancy related kidney injury group, with 92% of patients obtaining renal recovery. Seventy-nine percent of patients with malaria and kidney injury had renal recovery. The largest proportion of patients that transferred to ROPD and had dialysis discontinued despite failing to recover renal function comprised those with obstructive uropathy, accounting for 58% of this group. This group comprised predominantly of older patients with chronic co-morbidities and malignancies.

3.5.4 HIV infection and outcomes

3.5.4.1 Outcomes in HIV positive patients

Figure 12: Outcomes in HIV positive patients (N=83)

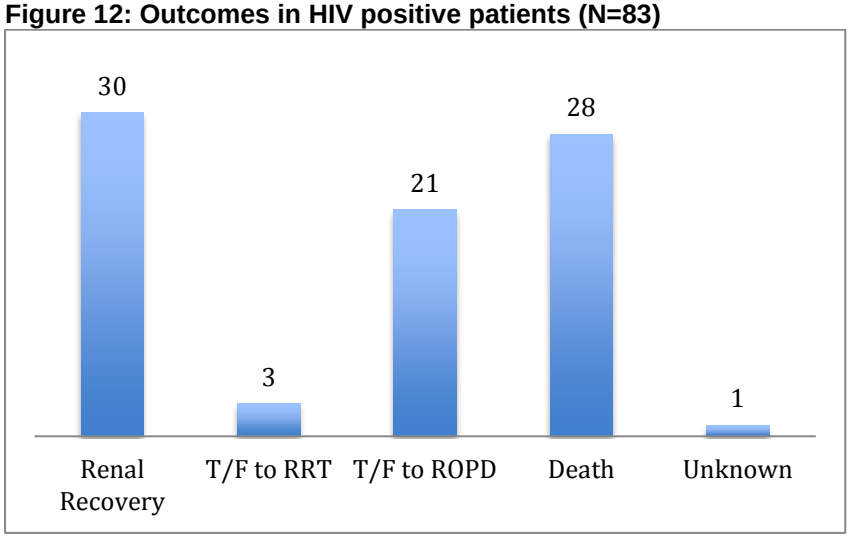


Figure 12 illustrates the outcomes of HIV positive individuals. 30 patients (36%) had renal recovery, with a similar proportion demising [28 patients (34%)].

Table 19: Outcomes in HIV positive vs HIV negative patients

	Renal Recovery	Transfer to chronic RRT	Transfer to ROPD	Death	Loss to follow up
HIV Positive (N=83)	30 (36%)	3 (4%)	21 (25%)	28 (34%)	1 (1%)
HIV Negative (N=221)	58 (26%)	71 (32%)	46 (21%)	42 (19%)	4 (2%)

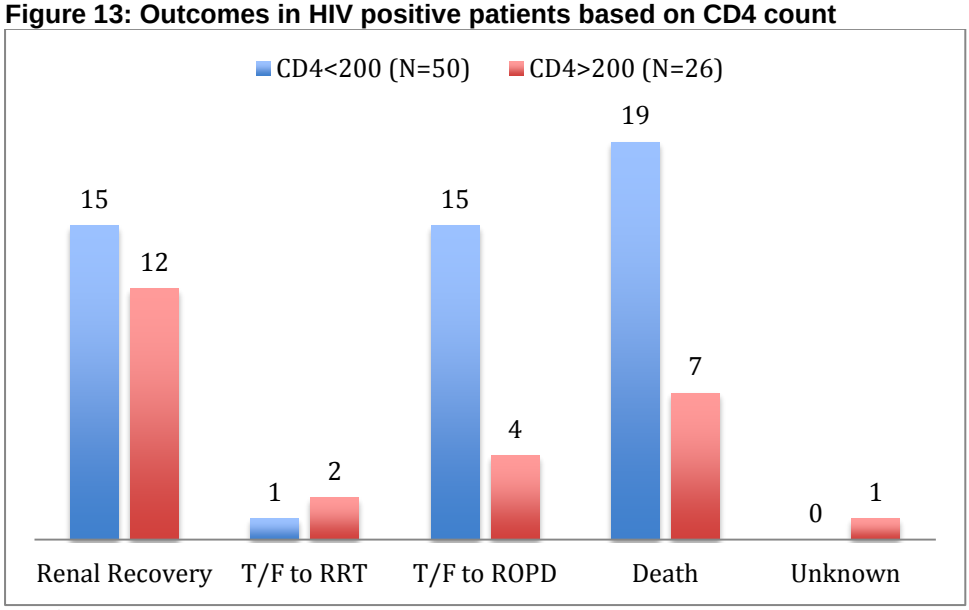
Chi^2 28.3; dF=3; p value<0.0001

A comparison of HIV positive and negative individuals is shown in Table 19. Renal recovery occurred in 58 patients (26%) of HIV negative patients; HIV positive patients had a better rate of renal recovery with 36% of HIV positive patients showing renal recovery (p<0.0001). Death as an outcome in both groups showed rates of 19% in HIV negative group and 34%

in HIV positive group (p<0.0001). A small proportion of HIV positive patients (4%) was transferred to the chronic RRT compared to 71 patients (32%) in the HIV negative group. There was a statistical difference between outcomes in these two groups (p <0.0001). Twenty-one percent of HIV negative patients were transferred to ROPD and cessation of their dialysis compared to 25% of HIV positive individuals.

3.5.4.2 Outcomes in HIV positive patients based on CD4 counts

Figure 13: Outcomes in HIV positive patients based on CD4 count

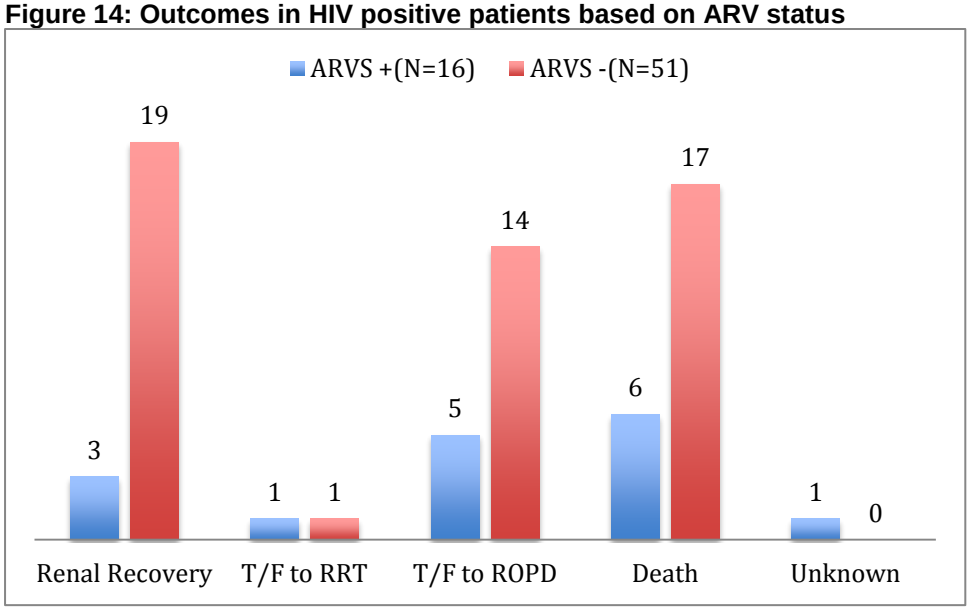


Chi^2=4.77; dF=3;P=0.1894

The CD4 counts of HIV positive individuals were noted with 7 of the 83 patients having an unknown CD4 count. There were 50 patients that had a CD4 count of less than 200 and 26 patients had a CD4 count greater than 200. Fifteen patients (30%) with a CD4 count of less than 200 had renal recovery compared with 12 patients (46%) in the CD4 count greater than 200. 19 patients (38%) with lower CD4 demised compared to 7 patients (26%) in the higher CD4 count group. There was no statistical significance between the two groups for all outcomes (p value=0.1894).

3.5.4.3 Outcomes in HIV positive patients based on ARV status

Figure 14: Outcomes in HIV positive patients based on ARV status



P value=0.5857

Antiretrovirals have become the mainstay and most effective treatment of choice in HIV infection. Sixteen patients (19%) were on ARVS at the time of diagnosis of the renal injury, with only 3 (18.5%) of these patients showing recovery and 6 (37.5%) demised. The majority of patients were not on ARVS (51 patients, 61%). Renal recovery occurred in 19 patients (37%); however a significant proportion demised (33%). There were no statistical differences of all outcomes between the two groups (p value=0.5857), probably due to the small sample size.

CHAPTER 4: DISCUSSION

4.1 Demography of patients presenting for acute dialysis

South Africa has a diverse population with various social and political influences that have changed patterns of disease and patient profiles within our hospitals. The mean age of presentation was 40 ± 13 years. The age of presentation is consistent with other developing countries. A retrospective review of patients with AKI in a North Indian tertiary institution showed that the mean age of presentation of AKI was 39 ±14 years (117). A similar review done in Saudi Arabia had a mean age of 33.7 ± 10.1 years(124). This is in contrast to first world countries. An epidemiological study of AKI done in Madrid, Spain had an average age of 64 ± 17 years (28). A United Kingdom based study had over 90% of its cohort being greater than 70 years of age (125). The large difference in age is directly related to the various patterns of disease that is seen between first world and third world countries. This is in contrast to the disease profile that occurs in developing countries of the world. Factors such as infective causes and pregnancy-related kidney injury also occur in increasing frequencies within the developing countries, resulting in the large discrepancy between the age groups.

Males accounted for 57% of the cohort. This closely resembles the findings of patients with HIV and AKI at a Johannesburg hospital; Vachiat et al had a 56% male predominance in his cohort (40).

Race has been a major discriminating factor in the history of South Africa. Various important factors over the last 100 years have affected the epidemiology of disease in

South Africa. CHBAH is situated in the heart of Soweto, a bustling area with a population of more than 1.5 million residents, of which the predominant race is black African. This large population accounts for the predominant race that feeds into the CHBAH drainage areas, with 92.3% of patients being black African.

Infective disease screening prior to dialysis is often done, in particular HIV, hepatitis B and hepatitis C. Eighty-three patients (26%) were HIV positive; 4% and 2% of patients had confirmed serology for hepatitis B and hepatitis C respectively; 6 % of the cohort had unknown HIV status, whilst the hepatitis B and hepatitis C unknown rates were much larger with more than 25% of patients not being tested for these infective diseases.

The prevalence of hepatitis B infection is estimated to be around 1% in South African urban areas (126). Our study noted a 4% rate of hepatitis B infection. A study conducted in Johannesburg clinics found a 5% rate of hepatitis B co infection with HIV (127). Three patients (3.6%) with HIV had co infection with hepatitis B.

The world wide incidence of hepatitis C is around 2-3% (128). Similar incidence is noted in our study with 2% of patients having Hepatitis C. The impact of HIV co infection was demonstrated by the CAESAR study. This multicentre study showed varying rates of HIV and hepatitis C co infection worldwide, with South Africa having a co-infection rate of 1.9% compared to rates as high as 48% in countries such as Italy (129). The HIV and hepatitis C co infection rate in our study was 1.2%, similar to the CAESEAR study figures.

4.2 Decompensated chronic kidney disease and co-morbidities

A large proportion of patients, 126 patients (39%), had an underlying chronic component to their decline in kidney function, with urgent need for acute dialysis. This group was defined as those patients that had a documented history or evidence of an underlying chronic reason for their kidney dysfunction and presented with an acute insult that resulted in rapid decline and need for acute dialysis.

The leading cause of underlying chronic co morbidity was hypertension. Sixty-six percent of patients in this group were diagnosed with hypertension and 90% of hypertensive patients were receiving treatment; 16 (19%) of the hypertensive patients were on treatment for more than 5 years. Diabetes mellitus accounted for a further 20% of patients in this group; 48% of these patients were on diabetic medication, either insulin or oral hypoglycaemics for more than 5 years. The decompensated chronic kidney group were all included in the analysis as they had an acute component at the time of initiation of dialysis.

4.3 Causes of acute kidney injury

The causes of AKI are often multifactorial with various aetiologies occurring in a single patient. Renal biopsy may be needed to give a definitive diagnosis. The underlying cause of kidney injury is often established on the basis of an adequate history and clinical features. It is supported by auxiliary investigations such as blood tests, radiological investigations and in some circumstances, more invasive procedures such as a biopsy. The causes of kidney injury found in our cohort are presented in Figure 11.

The majority of the patients (78%) with AKI requiring dialysis were referred from the medical wards. This is consistent with the audit done in India where medical patients accounted for 77% (117). Another audit carried out in the Himalayan region had close to 86% medical referrals (130) The study by Vachiat et al had 81% of patients referred from medical wards (40). Surgical and obstetric referrals for AKI and dialysis accounted for 12% and 8% respectively. Likely reasons for this large discrepancy include a selection bias against surgical and obstetrical referrals a large proportion of these patients present with pre renal dysfunction that can be treated conservatively, thus obviating the need for dialysis.

Seedat et al reviewed the causes of kidney injury in a South African population in 1978. This study showed that the leading cause of AKI was nephrotoxins (38). A subsequent audit a decade later by the same author showed that sepsis had replaced nephrotoxins as a leading cause of AKI (39). These findings are consistent with our cohort as sepsis accounted for 32.4% of AKI. AKI due to ATN was documented in 124 patients (38.2%). The underlying causes of ATN included sepsis (106 patients), toxins/herbal ingestion (10 patients), pancreatitis (5 patients) and contrast induced nephropathy (3 patients). Higher rates of ATN as a cause of AKI were found in the Madrid study that showed ATN accounted for 45% of their causes of AKI (29).The leading cause of ATN in our study was sepsis, accounting for 32.4% of the total study group. Sepsis accounted for approximately 50% of cases in the Cape Town based audit (81), whilst in India, sepsis accounted for 33.3% (130).

Malaria complicated by AKI with subsequent need for acute dialysis accounted for 19 patients (6%). Malaria with co infection of HIV occurred as the third most common cause of kidney injury in HIV positive patients, resulting in 16% of HIV positive patients needing to be dialysed. Malaria remains a common cause of AKI particularly in most of Africa as noted by Naicker et al in an epidemiological review published in 2008 (34).

Acute kidney injury in pregnancy is still a major problem in developing countries. Pregnancy-related kidney injury accounted for 24 patients (7.4%) of our cohort. This included eclampsia (2 patients), pre eclampsia (18 patients), abruptio placentae (3 patients), and post partum haemorhage (1 patient). This rate of 7.4% has substantially decreased from previous audits done in South Africa which showed that pregnancy-related AKI accounted for 16% of all AKI requiring dialysis (95). Improved antenatal screening, quicker delivery of patients and better obstetric intervention may be responsible for this reduction in frequency over the last 20 years. The rates of AKI in pregnancy in centres in India range from 11-14.5% (94, 117). One-third of all pregnancy-related AKI were HIV positive, with pre eclampsia as the predominant cause of AKI in this group.

Obstructive uropathy occurred in 12 patients (3.7%). This is substantially lower than first world countries where rates of 10% noted in Spain (29). The likely reason for this marked discrepency includes most notably the established geriatric population in the first world nations, with obstructive uropathy occurring more commonly within this group. The elderly patients and in particularly those with malignancies may be overlooked for dialysis and

excluded from the public sector dialysis programmes, thus decreasing the frequency of these patients being acutely dialysed.

The incidence of rhabdomylosis secondary to trauma, also referred to as “sjambok injury” has increased in South Africa (131). 3 % of the patients dialysed had rhabdomylosis complicated by AKI requiring dialysis. All of the 10 patients had developed rhabdomylosis secondary to violent injury and were admitted to the trauma unit.

Nine patients developed AKI requiring dialysis secondary to drug interactions. 2 of these patients had biopsy confirmed tubulo-interstitial nephritis; 3 of the patients were HIV positive on Tenofovir ; 2 of the 9 patients had lithium overdose and required dialysis subsequently. The offending drug was unknown in 4 patients.

Malignancy and subsequent initiation of dialysis occurred in 11 patients. 6 of these patients were HIV negative whilst 4 were HIV positive and 1 had an unknown HIV status. The malignancies encountered included Non Hodgkins Lymphoma (3 patients), Multiple Myeloma (2 patients), Acute Myeloid leukemia (1 patient), Prostate cancer (2 patients), Primary Brain tumour (1 patient) and Renal cell carcinoma (2 patients).

4.4 HIV and kidney injury – Demography and clinical data

HIV positivity accounted for 83 patients (26%) of our cohort. The mean age of presentation was 39 ± 11 years. This is consistent with the study conducted in Charlotte Maxeke Academic Hospital in Johannesburg which had a mean age of 38±9 years (40). There were no gender differences within the HIV positive group. The median CD4 count for all patients with HIV was 153 with a range of 4 to 621, consistent with the Johannesburg study that had a median CD4 count of 135. Hepatitis B and C co infection with HIV occurred in 3.6% and 1.2% of the HIV positive group respectively.

Antiretrovirals have become the mainstay of HIV management, both around the world and in South Africa. Of the 83 patients with HIV, 16 patients (19%) were on ARVs whilst 52 patients (62%) were not on ARVs at time of admission and initiation of dialysis. This is consistent with a previous South African study that had 17.1% of patients on ARVs (81). The mean CD4 count of patients on ARVs was 240 (range 106-621) compared to the ARV naïve group with a median CD4 count of 83 (range 4-572).

The causes of kidney injury in HIV positive and negative patients are outlined in Table 10 and 11. HIV positive patients most frequently had kidney injury secondary to ATN due to sepsis. This occurred in 53 patients (63%) of HIV positive patients. Vachiat et al found that sepsis accounted for AKI in 62% of the HIV positive patients compared to 43% in the HIV negative group (40).

HIV related kidney injury occurred in 44 of the 83 patients (53%). This was diagnosed on either biopsy or clinical suspicion which was confirmed with other auxillary investigations such as sonographical findings, urine PCR and blood investigations. These rates are similar to previous studies done at CHBAH in 2006 which showed incidence rates of 27% and 21% of HIVAN and HIVICK respectively (70).

4.5 The pre-dialysis blood urea and serum creatinine and outcomes

Initiation of dialysis is often based on clinical grounds and biochemical changes. Our study assessed the pre-dialysis blood urea and serum creatinine on the day that dialysis was initiated. These values were compared to outcomes. The pre-dialysis blood urea and serum creatinine levels are represented in Table 15 and 16 respectively.

The pre-dialysis blood urea was significantly lower in the group that had renal recovery ($p < 0.0001$). The mean blood urea level for patients with renal recovery was 34±19 mmol/l. This was much lower compared to the other groups; 49±20 mmol/l(transfer to chronic renal replacement), 51±22 mmol/l(transfer to ROPD), 45±23 mmol/l (death). A study in Belgium showed that there was no significant difference in the level of blood urea at dialysis and relationship to outcomes (132). This retrospective review, however, was done exclusively in an ICU setting and hence has limitations regarding extrapolation to our study population. Another study by Liu et al showed that blood urea levels at time of initiation had a strong correlation with mortality measured at 60 days after initiation of dialysis (109). This finding is

strongly supported by our study as the lower the urea at initiation of dialysis, the better the outcome.

Serum creatinine levels form the baseline of the widely used RIFLE criteria (11). In addition to pre-dialysis blood urea levels, our study evaluated the pre-dialysis serum creatinine levels and compared this to outcomes. All groups had a substantially lower serum creatinine level at initiation of dialysis for renal recovery compared to other groups that did not recover renal function. The Cape Town study that assessed HIV positive patients, showed that better outcomes were observed in patients that had pre-dialysis serum creatinine levels of <1230 µmol/l. This study showed that renal recovery occurred with a median pre-dialysis serum creatinine level of 902 µmol/l compared to a pre-dialysis serum creatinine of 1022 µmol/l for patients that required chronic renal replacement and levels of 937 µmol/l for those that demised (81). In our cohort, the average pre-dialysis serum creatinine for HIV positive patients with renal recovery was 805 µmol/l compared to serum creatinine of greater than 1000 µmol/l for both patient groups, that were either transferred to chronic renal replacement or demised.

4.6 Outcomes in all patients with kidney injury

The outcomes measured in our study were defined as renal recovery, transfer to chronic RRT, transfer to ROPD, Death or loss to follow up. The mortality rate was 23%. Previous studies done in India had mortality rates of 26.7% and 29.2% respectively (117, 130). Overall mortality rates from a developed countries as seen in the Madrid study had similar mortality rates from AKI of 26.7% (29).

Renal recovery was achieved in 98 patients (31%). Similar findings were observed in the Cape Town study with renal recovery independent of dialysis of 33.3% (81). In a large population based study conducted in Alberta, Canada, 61.8% of patients with AKI had renal recovery (116). Transfer to chronic renal replacement therapy occurred in 23% of our cohort. This is slighty more than the Indian study that showed that 15% of patients required chronic dialysis (117). The large numbers in our study is directly related to the greater proportion of patients that had already established chronic kidney disease with an acute component, likely accounting for the difference.

The highest mortality was noted in the HIV related kidney disease and ATN groups with 43% and 41.9% respectively. Sepsis was the major contributor to the ATN group. This is consistent with the Indian studies that had rates from 24%-46% (117, 120). The underlying cause of sepsis was not reviewed in our study.

Pregnancy induced kidney injury had the highest rate of renal recovery, with 92% of patients recovering their kidney function and 0% mortality rate. This group also had the lowest pre-dialysis serum urea and creatinine compared to all other groups, as expected due to the hyperfiltration seen in pregnancy as well as increased surveillance for dialysis in this group. 79% of patients with malaria and AKI had recovery of their kidney function. This rate was slightly lower than observed in a prospective study by Shukla et al that showed an 86% renal recovery rate (133). The mortality rate for malaria with AKI ranges from 15-50% (87). Our mortality rate for malaria with AKI was 5%; this difference in mortality is largely related to the exclusion of patients that were solely admitted to ICU.

4.7 Outcomes based on HIV status

Thirty patients (36%) in the HIV positive group had renal recovery compared to 58 patients (26%) who were HIV negative. The HIV negative group however had a lower mortality with only 19% demising compared to 34% in the HIV positive group. These findings were statistically significant (p value <0.0001). This is similar to findings elsewhere in the world, with rates ranging between 26%-43.3% (80, 134). In South Africa, Arendse et al found a 33.3% recovery rate, however this study had a higher mortality rate of 41% (81). Vachiat et al showed a mortality rate of 44% but showed no statistical difference in outcome between HIV positive and negative patients that were dialysed.

The CD4 counts were also reviewed and compared to outcomes. 46% of patients with CD4 counts of greater than 200 cells/µl had renal recovery compared to 30% of patients with CD4 counts less than 200 cells/µl. Lower CD4 counts also contributed to a higher mortality of 38% compared to their counterparts with higher CD4 counts that had a mortality rate of

26%. Our study showed no statistical significance (p value 0.5857) between patients that had AKI and CD4 less than 200 cells/µl and CD4 greater than 200 cells/µl. The Cape Town based study showed a better outcome in patients with AKI and CD4 counts greater than 200 cells/µl (81).

Patients' ARV status and relationship to outcomes were also assessed. Patients that were not on ARVs at the time of initiation of dialysis had a 37% rate of renal recovery compared to 19% in patients that were on ARVs. The mortality rate of patients on ARVs was slightly higher than those patient not on ARVs (37.5% vs 33%); this finding however was not statistically significant (p = 0.5857) and is likely related to the low numbers in the two groups. Arendse et al reported a mortality rate of 22.9% for patients on ARVs (p =0.133) (81).

4.8 Limitations

This was a retrospective review of all patients that were dialysed acutely at CHBAH and hence several limitations are evident. The records were reviewed from a computer based system, known as BART. The input of variables is subject to the attending doctor in charge of the case. Variables such as the hepatitis serology and ARV status were not well captured and may well have an influence on some analyses.

Another important confounder was the large group of 'Decompensated chronic kidney disease'. This large proportion of patients included those that had a documented element of chronic kidney disease and were initiated on dialysis. The reasons for the acute deterioration of renal function in this group were not subanalysed.

The “transfer to ROPD” group included all patients whereby acute dialysis was stopped in patients that did not achieve renal recovery. The eGFR at the cessation of dialysis was not evaluated and hence patients that were in a stable state, albeit still chronic were not separately evaluated, leading to biasness.

Definitive causes of kidney disease in the HIV positive group were not established on basis of biopsy. This is a major limitation, particularly when assessing the ‘HIV related kidney disease” group that comprised of HIVAN and HIVICK, which can only be diagnosed definitively by histology, but were assessed on the basis of other auxiliary investigations in making a presumptive diagnosis. HIV related chronic kidney disease would be a better reflection of this group.

The numbers of patients that were subanalysed in certain groups such as HIV positive patients were not large. This, as seen in the ARV status and outcomes may not be a true reflection of the relationship.

ICU makes up an integral part of any hospital and AKI in the critically ill patient makes up a large percentage of this disease profile in hospitals. The exclusion of patients admitted to ICU and managed for AKI was not reviewed in this study and hence would have skewed mortality and outcomes.

Outcomes were defined in 5 groups which included renal recovery, transfer to chronic RRT, transfer to ROPD, death and unknown outcomes. Renal recovery however was assessed as normalization of renal function and independence of dialysis at a point in time. A repeat

serum creatinine for all outcomes was not assessed at a 3 month interval from initiation of dialysis and hence cannot truly reflect the definition of AKI according to the RIFLE criteria.

4.8 Recommendations

Acute kidney injury is a common presentation of disease within our setting. Further studies need to evaluate the actual number of patients with AKI in our hospitals irrespective of the initiation of dialysis and relate this to outcomes. Closer monitoring of blood urea and serum creatinine particularly after 3 months needs to be assessed, so that the fulfillment of the RIFLE criteria for AKI can be established. A prospective study design assessing these parameters is recommended.

4.9 Conclusion

Acute kidney injury with subsequent initiation of dialysis is a major component in medical practice and has a high mortality rate. Economic and social factors play a massive role in initiation of dialysis in South African state health care facilities. Our audit shows that the leading causes of AKI with subsequent initiation of dialysis included decompensated chronic kidney disease, ATN, pregnancy induced kidney injury, malaria, HIV related kidney injury and GN. Acute tubular necrosis was the one of leading causes in both HIV positive and negative patients with a high mortality rate in both groups. HIV positive patients had a higher renal recovery rate compared to their HIV negative counterparts, however mortality was overall higher in HIV positive patients; however those with higher CD4 counts had an

overall improved outcome. Earlier dialysis had a superior outcome in all patients, including HIV positive patients.

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CHAPTER 6: APPENDIX

APPENDIX A: Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Mohammed Variava

CLEARANCE CERTIFICATE	**M120413**
PROJECT	A Retrospective Review of the Profile and Clinical Course of Patients Requiring Acute Dialysis at Chris Hani Baragwanath Hospital over a 2 year period
INVESTIGATORS	Dr Mohammed Variava.
DEPARTMENT	Internal Medicine/Dept of Nephrology
DATE CONSIDERED	04/05/2012
DECISION OF THE COMMITTEE*	

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor :

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

Appendix B: Data Collection Sheet

Allocated Study number:_____ Patient Number:_____

Age:_____

Sex:	Male	Female

Race:	African	Coloured	White	Indian

HIV Status:	Positive	Negative	Unknown

If Positive: CD4 Count:_____

If Positive: ARV Status: Yes No

If ARV status Yes:Duration_____

Hepatitis B	Positive	Negative	Unknown
Hepatitis C	Positive	Negative	Unknown

Pre-dialysis Blood urea:_____
Pre-dialysis Serum creatinine:_____

Underlying Primary Disease: 1._____ 2_____3_____4_____

Underlying chronic comorbidities:

Hypertension	Yes	No
Diabetes	Yes	No
Malignancy	Yes	No
Other:_____	Yes	No

Discipline of referral:	Med	Surg	Obs & Gynea	Other

Outcomes:			
	Renal Recovery	Yes	No
	Transfer to chronic RRT	Yes	No
	Transfer to ROPD	Yes	No
	Death	Yes	No
	Loss to follow up	Yes	No

Appendix C: Turnitin Letter from Supervisor