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Severe Acute Renal Failure at Groote Schuur Hospital

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August 2002.

Dedicated to:

My beautiful wife and children: Diana, Isabella and Max

Contents

Acknowledgements

I would like to thank all the members of the renal unit at Groote Schuur Hospital for their ongoing support and encouragement during the time that I carried out this study.

Declaration

I, Piers Alexander Stead, hereby declare that the work on which this thesis is based is my original work (except where acknowledgement indicates otherwise) and that neither the whole work, nor any part thereof, has been, is being, or is to be submitted for any other degree in this or any other University.

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Acute renal failure:

Acute renal failure (ARF) is a syndrome occurring over hours to days of renal dysfunction with a reduction in glomerular filtration rate (GFR) resulting in a failure to excrete nitrogenous waste products.

Acute renal failure is responsible for five percent of hospital admissions and 30 percent of admissions to the intensive care unit (Hou, Bushinsky et al. 1983). Regardless of the cause it is an independent risk factor for death. It is, therefore, not only an important field of study because of the work load in any tertiary hospital but also because of the direct impact it has on patient outcome.

The problem of acute renal failure has not been well studied in African countries. Studies from both developed and developing countries show that acute tubular necrosis (ATN) is the commonest cause of ARF. This thesis will aim to outline the pathophysiology of ATN as it is currently understood. It will then review the results of the patients who presented to Groote Schuur Hospital between July 2000 and June 2001 and required acute dialysis.

Acute Tubular Necrosis

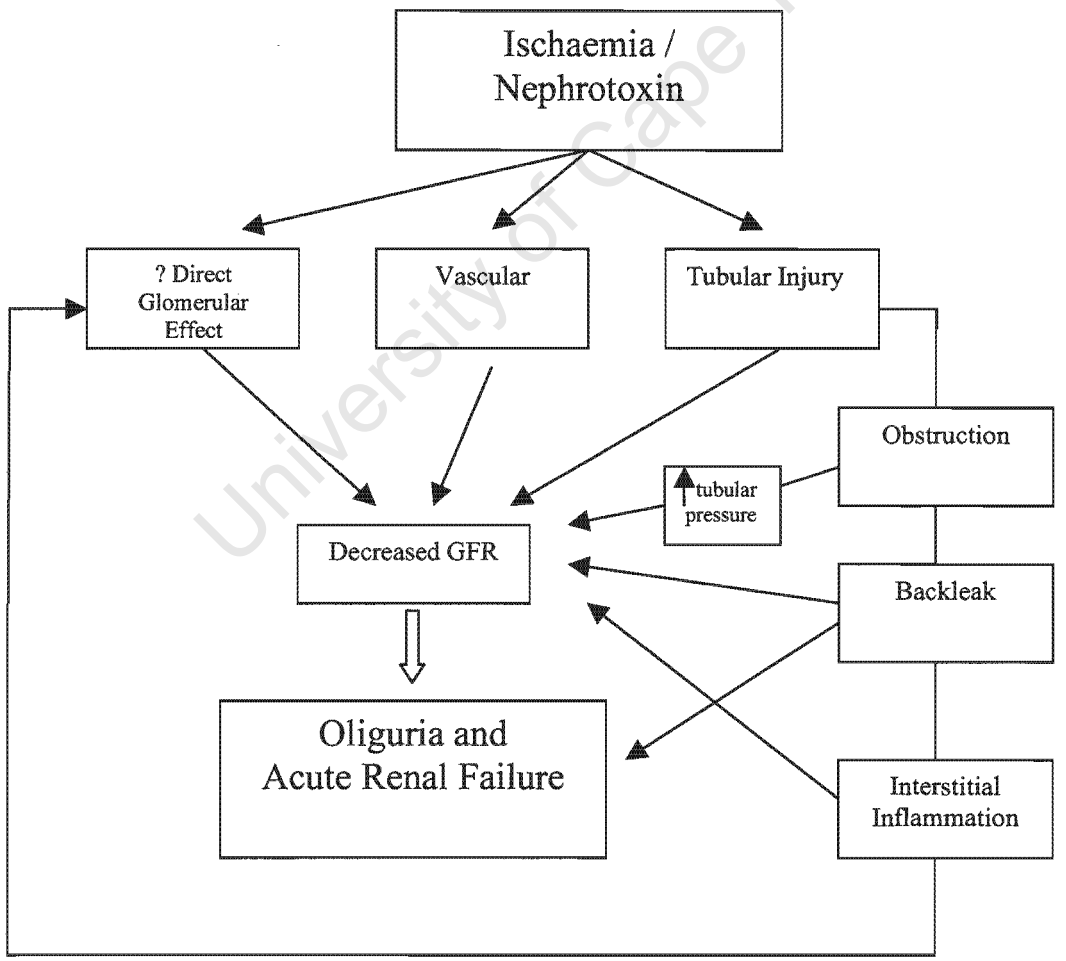
Ischaemic and toxic injury resulting in acute tubular necrosis (ATN) accounts for over 90% of cases of intrinsic acute renal failure (Hou et al. 1983). The mortality remains high. There is no specific treatment for ATN, reflecting our incomplete understanding of the pathophysiology of the disease process. The regenerative healing process is complicated, involving cytokines and growth factors, which regulate high rates of DNA and cell synthesis. Many of these processes mimic those that are seen during organogenesis (Safirstein 1999). A better understanding of the pathogenesis of the injury and the recovery process will hopefully lead us to develop therapies that improve the outcome.

In over 50% of patients with hospital acquired ATN the cause is multifactorial. The aetiology can be accounted for by iatrogenic factors in fifty-five percent of these patients (Hou et al. 1983). There will be no obvious episode of hypotension documented in up to 50% of patients with established post-operative ATN (Hou et al. 1983). Sepsis and the inflammatory response may contribute to and exacerbate systemic vasodilatation and intra-renal vasoconstriction.

In ATN there is established injury to the renal parenchyma. This injury may range from mild tubular cell injury to extensive, irreversible cortical necrosis. Ischaemia results from systemic hypotension and intra-renal vasoconstriction to the extent that the auto-regulatory mechanisms fail and blood flow to the renal tissue is compromised. The site of the injury is still under debate. It was for many years thought to be the loop of Henle and the distal tubule but more recently, consensus

holds that the highly metabolically active proximal convoluted tubule (PCT) and the thick ascending loop of Henle (tALH), both lying in the outer medulla, bear the brunt of the injury (Lieberthal and Nigam 1998).

The kidney is at particular risk for toxic injury as it receives twenty five percent of the cardiac output and also concentrates many potential toxins by the counter current mechanism and also the presence of specific transporters on the tubular epithelial cells. These toxins may be either extrinsic (eg drugs) or intrinsic (eg haem containing compounds.



Pathophysiology of ATN adapted from (Lameire and Vanholder 2001)

Vascular: Vasoconstriction/ Loss of Auto-regulation

Systemic hypotension or direct intrarenal vasoconstriction caused by certain drugs (intravenous contrast agents, calcineurin inhibitors) is mediated via the effects of angiotensin II, serotonin, sympathetic renal nerve stimulation and probably most importantly via the effect of endothelin (Lameire and Vanholder 2001). Not only is there intrarenal vasoconstriction but also a loss of autoregulation. The outer medulla, in particular, has selective reduction in blood flow. This makes the kidney more susceptible to further, smaller insults, which translates into perpetuating the clinical course of ARF.

In the setting of systemic hypotension the blood flow is reduced by 80 percent in the outer stripe of medulla, where S_3 of the PCT is located. This is in contrast to the cortex where blood flow is reduced to 60 percent of normal. This markedly reduced medullary perfusion is contributed to in part by cytokine mediated increased capillary permeability. This results in fluid extravasating into the extra-capillary compartment and thereby resulting in intracapillary haemoconcentration. This contributes to sludging and aggravation of the decreased medullary perfusion (Nath and Norby 2000). Preliminary studies have been carried out in rats giving a single intravenous injection of umbilical vein endothelial cells after aortic cross clamping. These healthy endothelial cells implant into the damaged renal microcirculation and protect against/speed recovery of ATN (Goligorsky et al. 2002).

Endothelin:

Endothelin is the most powerful endogenous vasoconstrictor. It causes vasoconstriction of both efferent and afferent arterioles, affecting pre and post glomerular blood flow. There has also been evidence to show that endothelin acts as an autocrine growth factor in PCT cells in vitro (Wilhelm et al. 1999). Endothelin-1 gene is upregulated in the peritubular capillaries after an acute ischaemic insult. This is stimulated by the initial ischaemic insult but reperfusion serves to perpetuate and sustain the upregulation (Wilhelm et al. 1999). Endothelin mediates its effect via two receptors: ET_A and ET_B. Initial work suggested that ET_A stimulation resulted in vasoconstriction and ET_B stimulation in vasodilatation. More recently, however there is evidence that both ET_A and ET_B are vasoconstricting and the degree is dependent on which vascular bed is studied (Wang et al. 2000). Evidence from rat studies showed that the use of selective endothelin receptor ET_A blockade resulted in improved blood flow and mitigated against the development of ATN (Gellai et al. 1994). A multicentre trial, with 158 patients, looked at the protective effects of a non-selective endothelin receptor blockade. All patients had chronic renal impairment and received radiocontrast agents for coronary angiography. The treatment arm, however, showed a worse outcome over those receiving placebo. In the treatment group there was a higher incidence of side effects, most importantly hypotension. Other explanations may include the possibility of altered endothelin physiology in patients with renal impairment, particularly as over 60% of these patients were diabetic (Wang et al. 2000).

Serotonin:

Serotonin (5-hydroxytryptamine, 5-HT) may also play an important role in interfering with normal vascular autoregulation. Serotonin acts via seven different receptors. 5-HT_2 receptors mediate platelet aggregation and smooth muscle contraction. Particularly in the post ischaemic kidney 5-HT_2 receptor-mediated vasoconstriction may exacerbate the injury. The ability to block this effect with ketanserin, a serotonin blocker, results in improved autoregulation and attenuation of the injury in the experimental setting (Verbeke et al. 1998).

Vascular Reactivity:

In an attempt to further delineate the basis for the altered vascular reactivity a study was done in rats looking at F-actin in vascular smooth muscle cells. This showed that there was little damage to F-actin after 15 or 45 minutes of ischaemia but that injury was associated with reperfusion and occurred three hours post reperfusion. It is postulated that the disorganisation of actin (cf tubular cytoskeleton below) is in part responsible for the altered vascular reactivity which occurs post ischaemia-reperfusion injury (Kwon et al. 2002).

Adenosine:

Animal experiments also suggest that adenosine plays a role in the mediation of vasoconstriction, particularly after administration of intravenous contrast agents. There is increased oxygen consumption and decreased ATP with adenosine being produced as a by product of this effect. A study using the adenosine receptor antagonist theophylline failed to show any clinical benefit over placebo (Erley et al.

1999). The study did show significant reduction in N-acetyl-β-glucosaminidase enzymuria in the treatment arm. This is a marker of tubular damage. Unfortunately (or fortunately for the patients) only 1 of the 29 patients in the placebo arm suffered a significant deterioration in renal function thereby making it difficult to show any benefit in the treatment arm.

Angiotensin II:

Despite there having been many advances in the understanding of the role of angiotensin II in disease, its role in the pathophysiology of acute renal failure has not been well clarified.

Prostaglandin E_1:

Animal studies show that prostaglandin E_1 not only has a direct vasodilating effect but also inhibits the transcription of endothelin and has a cytoprotective effect. This resulted in a small pilot study being carried out looking at the protective effect of PGE_1 in patients receiving intravenous contrast. The placebo group had significantly higher elevation of serum creatinine, especially in the intermediate dosing group, but no clinically relevant changes in creatinine clearance were observed (Koch et al. 2000).

Role of Inflammatory Infiltrate:

After an ischaemic or toxic insult there is an increase in the number of leukocytes within the kidney. They may exacerbate the injury by the release of reactive oxygen

species (ROS) and proteases. This inflammatory infiltrate is largely absent within the first 12-24 hours post ischaemia. There is however already evidence of leukocytes adhering to the endothelial lining (Ysebaert et al. 2000). Neutrophils are generally considered to be harmful where as phagocytes appear to be important in the repair process. Intravascular neutrophils may already start to do their damage within the first 24 hours by releasing myeloperoxidase, interfering with microcirculation. This has been labelled the "hit and run" phenomenon (Ysebaert et al. 2000).

Intercellular adhesion molecule 1 (ICAM-1) plays a pivotal role in the endothelial adhesion and trans-endothelial migration of leukocytes into the interstitium. Studies looking at blocking ICAM-1 with anti-ICAM-1 antibodies or in knockout mice show protection against ischaemic ATN (Lameire and Vanholder 2001).

By five to ten days after an ischaemic/reperfusion injury the mononuclear cell becomes most prominent with fewer neutrophils and helper T-cells (and almost no B-cells). This inflammatory infiltrate is most prominent in the outer stripe of the medulla (Ysebaert et al. 2000).

Reactive Oxygen Species (ROS):

The kidney is a highly metabolically active organ accounting for ten percent of the body's oxygen consumption. As a by-product of normal oxidative metabolism it produces low levels of ROS. Inordinate production of ROS which occurs in the setting of ARF is however injurious to the kidney. In the post ischaemic kidney there

is depletion of glutathione which is a thiol anti-oxidant and normally contributes to the detoxification of peroxides.

The majority of our understanding of the role of ROS in ATN comes from experimental models. The most commonly implicated ROS include superoxide anion, hydrogen peroxide, hydroxyl radical, and more recently implicated are nitric oxide and the peroxynitrite anion (Nath and Norby 2000).

These ROS may cause either vasoconstriction or vasodilatation depending on the type of ROS and their rate of production. They may also directly affect vascular reactivity or act via the production of other vasoactive substances. ROS may increase the production of eg endothelin, isoprotanes (by-product of non-enzymatically oxidised arachidonic acid) or thromboxanes or inhibit the action of vasodilators. They also contribute to the impaired autoregulation of blood flow in the post ischaemic kidney.

Basic cellular components can all be altered by ROS with a resultant profound effect on cellular functioning. ROS activate phospholipase A_2, degrading phospholipids in cell and organelle membranes. Increased membrane porosity results in efflux of intracellular and influx of extracellular substances, disrupting the normal homeostasis of the cell. With impaired mitochondrial functioning and also limitation of glycolysis-dependent generation of ATP there is impaired functioning of transmembrane pumps and impaired integrity of the cytoskeleton. Increase in intracellular sodium results in cellular swelling and resultant tubular obstruction and decreased vascular flow.

ROS can activate NF-κB and upregulate the production of proinflammatory interleukin- 8, MCP-1 and RANTES. ROS also increase the expression of ICAM-1 on endothelial cells. This results in increased leukocyte adhesion to the endothelium and subsequent transendothelial migration, which potentiates the inflammatory infiltrate.

In low concentrations ROS may be protective. ROS may be responsible for increasing the expression of growth factors: EGF-1, HGF, IGF-1. There is also evidence for the induction of p21 cyclin dependent kinase inhibitor, which inhibits apoptosis (Nath and Norby 2000).

The role of nitric oxide (NO) is complex, depending on concentration and site of production. Our current models of ARF still fail to accurately delineate the exact role of NO. At high levels its effects may be completely opposite to those at low levels. It is constitutively produced at low levels by eNOS (endothelial NO synthase). At these levels it is secreted in a pulsatile fashion and mediates vasodilatation and is anti-apoptotic. Inducible NOS (iNOS) is upregulated and an important mediator of ischaemic injury. These effects appear to be mediated via the peroxynitrite anion. This anion results in direct DNA damage and lipid peroxidation (Goligorsky et al. 2002). iNOS knock out mice are protected from hypoxic injury. Targeting of iNOS mRNA with antisense oligonucleotides prevents iNOS induction and the resultant cytotoxic effects (Noiri et al. 1996).

Platelet Activating Factor (PAF):

PAF is produced by not only the endothelial cells but also by mesangial cells. In low concentrations, via the increased production of NO, it may vasodilate constricted

arteries. In higher concentrations it results in afferent arteriole vasoconstriction and mesangial cell contraction. It also affects endothelial cell permeability and may directly cause cellular toxicity. All of these factors decrease renal blood flow and increase tubular fluid back leak resulting in a drop in the GFR (Lopez-Novoa 1999). Cyclosporin, cisplatinum and gentamicin toxicity are all in part mediated through the effect of PAF.

When antagonists to PAF are given to experimental rats there is a protective effect as long as the drug is given before or within 30 minutes of the ischaemic insult. There was no added benefit when this was given in combination with anti-ICAM-1, postulating that PAF may also play a role in leukocyte-endothelial interaction (Lameire and Vanholder 2001).

Melanocyte Stimulating Hormone (MSH):

α MSH is anti-inflammatory and inhibits the migration of neutrophils (Nath and Norby 2000). It also inhibits the production of cytokine induced NO. In rats it has been shown to be protective against ischaemic ATN. Its role in humans has not clearly been delineated (Lameire and Vanholder 2001).

Tubular Injury:

Growth Factors and Gene Expression:

Recovery from ATN depends on normally quiescent cells entering into mitosis. There has been considerable research in animal models looking at both the expression of genes which encode for growth factors and also the use of exogenous growth factors

in the attempt to accelerate recovery from ATN. Despite this research our understanding still remains quite limited.

Growth promoting signals reach the nucleus via induction of immediate early (IE) genes: cfos (a proto-oncogene) and early growth response-1 (Erg-1). The increased expression of these genes is short lived. Rat studies have shown that after an acute ischaemic episode there is increased expression of cytokine like genes JE and KC. These code for small cytokine like glycoproteins. There is an increase production of mRNA of JE and KC genes which occurs almost immediately after the ischaemic insult. KC peaks at one hour post ischaemia and returns to normal by 24 hours and JE peaks later at 48 hours and returns to baseline values at 6-7 days. These gene products are secreted by tALH and DCT and have chemokine qualities stimulating leukocyte infiltration. The JE gene product in the rat is equivalent to the human monocyte chemoattractant protein (MCP-1) and is localised to the tALH. They may also play a role in the migration of regenerating epithelial cells along the basement membrane (Safirstein et al. 1991).

Experimental studies in rats have shown that insulin like growth factor (IGF), epidermal growth factor (EGF) and hepatocyte growth factor (HGF) all accelerate recovery from acute renal failure. (Wang and Hirschberg 1997) As noted above most of the damage in patients with ATN occurs at the S_2/S_3 segment of the PCT and the tALH. These cells are normally in G_0 phase of the cell cycle. After an ischaemic insult they re-enter the cell cycle and the mitosis index increases by several orders of magnitude. These growth factors possibly stimulate cells out of the resting G_0 or inhibit apoptosis or possibly act via another mechanism. In recovering rat renal

tubules there is moderate increase in expression of TGF-β in the PCT (Gobe, Zhang et al. 2000). The exact role of this growth factor has not been clearly delineated in ATN in humans.

Most of the work has concentrated on the role of IGF-1. IGF-1 is widely expressed along the nephron except in the PCT. Receptors are abundantly expressed on both the basolateral and the apical membrane of the PCT cells. Rat studies show that there is a transient increase in IGF-1 in PCT cells and also migrating inflammatory cells, suggesting a paracrine action. In vitro studies show that IGF-1 decreases apoptosis and increases expression of EGF receptors. In both human and rat studies it also promotes renal blood flow via activation of iNOS. The use of rhIGF-1 in rats has been shown to accelerate recovery of post ischaemic ATN. The two human trials have unfortunately not been as positive. After abdominal aortic aneurysm repair there was only a trend towards improved outcome and in the other study patients with ATN post sepsis or shock there was no benefit demonstrated. (Wang and Hirschberg 1997)

HGF is expressed in interstitial cells in humans. There has been some work looking at the use of exogenous rhHGF in recovery of delayed allograft function in rats, mice and more recently a dog model (Wang and Hirschberg 1997).

Osteopontin expression is profoundly increased after an ischaemic insult. The exact role that osteopontin plays has not been clearly delineated. There is increased expression throughout the length of the tubule with some variation between proximal and distal tubules. It can bind to integrins and may play a renoprotective role during ischaemia-reperfusion insults (Lameire and Vanholder 2001).

Gene down regulation:

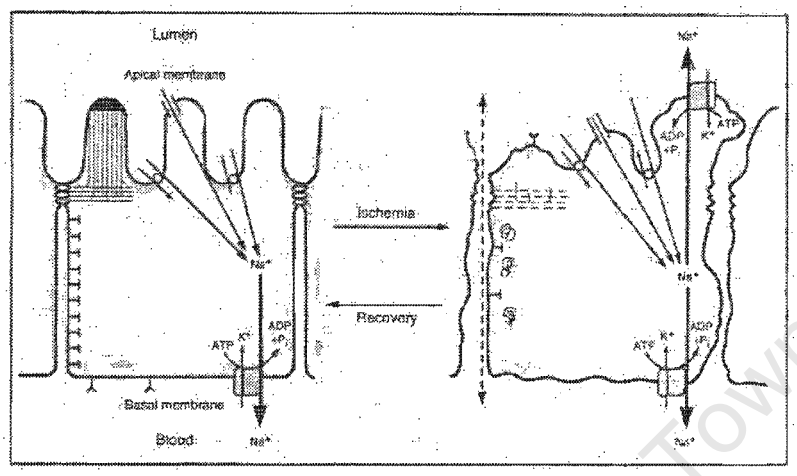
Three genes are down regulated after an acute ischaemic insult: preproEGF, Tamm-Horsfall and Kidney Specific Protein of 32 kDa size (KSP32d) (Hu et al. 2000) EGF and Tamm-Horsfall protein are only expressed by mature tubular cells.

EGF and its receptors are normally expressed in the DCT. After an ischaemic insult there is decreased expression in the PCT with a slow recovery to 50% of basal levels by day 21. In parallel with this is an increase in EGF receptor density. The exact role that EGF has to play in the post ischaemic injury is still poorly understood. (Safirstein et al. 1990) In rats the use of EGF has been shown to accelerate recovery from ATN (Wang and Hirschberg 1997) however it is known to be inhibitory in several cell types, including liver and kidney cells in neonatal rats (Safirstein et al. 1990). It has been proposed that the down regulation of these genes may serve to allow dedifferentiation of tubular cells to allow proliferation and restoration of the normal epithelial lining. A further renal specific protein has been identified: KSP32. It is expressed by PCT cells. The exact physiological function of this protein has not yet been determined but it is known also to be acutely down regulated within 24 hours of ischaemic insult to the kidney (Hu et al. 2000).

Cell Polarity:

Epithelial cell function is dependent on the structure and make up of the cell membrane. This structure is important in determining cell signal recognition and maintenance of cellular physiology. With ischaemic insults there is a time dependent graded injury. Initially, within 5 minutes, the lipid content of the membrane decreases

and the phosphatidyl-choline, -inositol content increases. After 10 minutes Na/K ATPase pumps lose their polarity, from being located on the baso-lateral membrane to become situated in the apical/brush border.



Redistribution of Na/K ATPase: adapted from (Fish and Molitoris 1994)

Despite their redistribution they still remain active. This results in Na being pumped back into the lumen, resulting in futile cycling and may contribute in part to the high urinary excretion of Na associated with ATN.

Leucine aminopeptidase is redistributed from the apical to the basolateral membrane. The redistribution of lipids in the cell membrane alters the properties of the membrane and interferes with function of the membrane proteins. This has been demonstrated to decrease the glucose transport into the cell.

As early as 1951 J Oliver showed that a proportion of detached tubular epithelial cells that are shed into the lumen are still viable. The exact pathogenesis of this cellular detachment is only now becoming understood and better defined. Integrins are transmembrane proteins with α and β subunits. The cytoplasmic domain is attached

to/forms part of the cytoskeleton. The extracellular domain is in turn attached to integrins of adjoining cells, forming tight junctions and to matrix proteins: collagen, fibronectin and laminin. This is mediated via a calcium dependent interaction with the arginine-glycine-aspartic acid sequence of the above mentioned matrix proteins (Fish and Molitoris 1994). Sub-lethal injury does not alter the total number of integrins expressed on the cell surface but interferes with their attachment to matrix proteins. In a similar fashion to the Na/K-ATPase pumps, they are redistributed from the basolateral to the apical cell membrane (Gailit et al. 1993). Tubular cells therefore detach from the basement membrane and in the tubular lumen, reattach to each other contributing to intratubular obstruction which is in part responsible for the oliguria of ATN. Detachment of tubular cells not only contributes to cast formation but also leaves the basement membrane denuded, allowing back leakage of glomerular filtrate.

Cytoskeleton:

The actin cytoskeleton plays a pivotal role in the maintenance of the different areas of the surface membrane and in cell-cell interaction. As cellular polarity is lost the actin of the cytoskeleton is redistributed from a circumferential, terminal web and microvilli location to become distributed throughout the cytoplasm. Microvilli are lost by internalisation, shedding into the lumen and membrane fusion (Fish and Molitoris 1994). Normal polymerisation of actin filaments is affected with G-actin being converted to F-actin. During recovery, F-actin is shed into the lumen and there is a correction of the G: F-actin ratio in the cytoskeleton.

With loss of normal cell-cell interaction the integrity of the tight junctions are compromised, allowing the back leak of fluid.

Calcium:

Following a hypoxic insult there is a rise in intracellular calcium. This is in part due to an influx of calcium into the cell but also, to a lesser degree, due to mobilisation of calcium from intracellular stores. This rise in calcium activates the calcium dependent cysteine protease calpain, which then degrades cytoskeletal proteins. Ankyrin and spectrin, which anchor Na/K ATPase, are disassembled, allowing for the change in cell polarity as mentioned above. As noted above renal ischaemia causes marked intrarenal vasoconstriction. In healthy or hypertensive patients calcium channel blockers are known to cause afferent arteriole vasodilatation.

In view of these calcium dependent events, calcium channel blockers have been used in an attempt to prevent or ameliorate post ischaemic ATN. Results are unfortunately conflicting and most of the studies showing benefit have been open or uncontrolled studies (Epstein 1992).

Apoptosis, Necrosis and Survival:

Cellular stress is followed by cell death via necrosis or apoptosis or cellular repair and survival. There is a balance between cytoprotective and cytoreductive forces. Two distinct pathways may stimulate the IE response. Each of these mediated via different members of the mitogen activated protein kinases (MAPK's). Growth factors stimulate extracellular regulated kinases (ERK's) and p21cyclin dependent kinase inhibitor. Cell cycling is arrested and there is time for cellular repair and subsequent proliferation. Counteracting this is the stimulation of stress activated protein kinases (SAPK's). These are stimulated directly by oxidative, hypertonic, chemical stress,

TNF or lipopolysaccharide (LPS). SAPK's stimulate activation of c-jun, which results in a cytoreductive response and apoptosis (Safirstein et al. 1998).

Tubular epithelial cell loss is in part due to apoptosis of these cells. Sixty minutes of renal ischaemia stimulates the activity of p38 MAPK. This is followed by increased levels of TNFα mRNA. This is one of the main stimulants inducing tubular cell apoptosis. The inhibition of p38 MAPK or the administration of TNFα antibody abolishes this response (Meldrum et al. 2001).

The DCT is relatively resistant to ischaemic insults. Transient ischaemic injury in rat kidney induces the production of heat shock protein (HSP) 72. Increased levels persist for days and confer a protective benefit against subsequent injury. Longer insults however, result in necrosis (Emami, Schwartz et al. 1991).

During an ischaemic insult levels of the proto-oncogene family Bcl-2 Bcl-X_L and Bax are low. Within 24 hours of reperfusion Bcl-2 Bcl-X_L and Bax are greatly increased in the DCT and expression of Bcl-X_L and Bax are increased in the PCT. Bcl-2 is anti-apoptotic and it is thought that this may protect the DCT from ischaemic injury and resultant apoptosis. Survival of the epithelial lining of the DCT allows for expression of growth factors, which is important for autocrine action within the DCT but also paracrine action in the PCT (Gobe et al. 2000). ROS may also induce the release of cytochrome C from mitochondria. This activates inactive caspases, which in turn results in degradation of the cytoskeleton and DNA, contributing to the process of apoptosis.

Apoptosis is an energy requiring process and will therefore only occur if there is sufficient ATP available. Between 15- 25 percent of normal levels are required for the regulated induction of pathways that result in apoptosis. Depletion of ATP to a greater degree than this results in cellular necrosis. Therefore in ATN there is a spectrum of apoptosis necrosis and survival of epithelial cells (Lieberthal et al. 1998). The surviving cells then forming the foundation from which the tubular epithelium is regenerated.

Conclusion:

Animal models, in vitro cell cultures and clinical studies have greatly furthered our understanding of the pathophysiology of ATN over the last twenty years. The treatment, however, still remains largely supportive. Many trials looking at new therapeutic agents have been at best unconvincing. Quite possibly we may need to use multiple agents to achieve clinical improvement in a condition that still has an unacceptably high mortality.

Aims and Methods

Aim: To assess the incidence, causes and outcome of all patients with acute renal failure requiring dialysis at Groote Schuur Hospital.

Methods: All patients admitted between July 2000 and June 2001 who required dialysis for acute renal failure were followed prospectively. Their demographics, including HIV status were recorded. The reason for renal failure and concomitant diseases and medications were noted. The indication for dialysis, type of intravenous access, duration of dialysis and complications of IV access were followed. Renal and patient outcome was followed up for one month after the last dialysis. Patients undergoing renal transplantation with delayed graft function were excluded from the study.

Results

One hundred and sixteen patients were dialysed acutely in the one-year period of the study. The mean age of the patients was 43.4 +/- 15.2 years. The age distribution is shown in figure 1. The majority of patients were male, 67 with 49 female patients. There was no significant difference in age between the male and female patients. Patients from medical wards were younger than the surgical patients, 42.9 +/- 14.4 and 46.8 +/- 15.5 respectively. The obstetric patients had a mean age of 26.8 +/- 7.5.

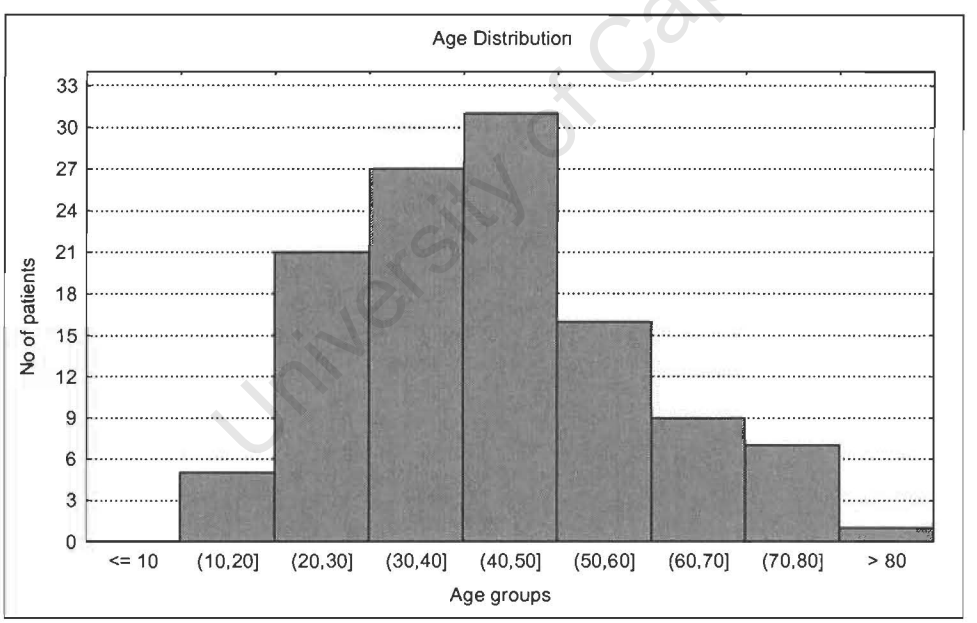


Figure 1

The male- female distribution varied with respect to the discipline under which the patients were admitted. (Figure 2) The greatest disparity being in the SICU where the male to female ratio was 21:7.

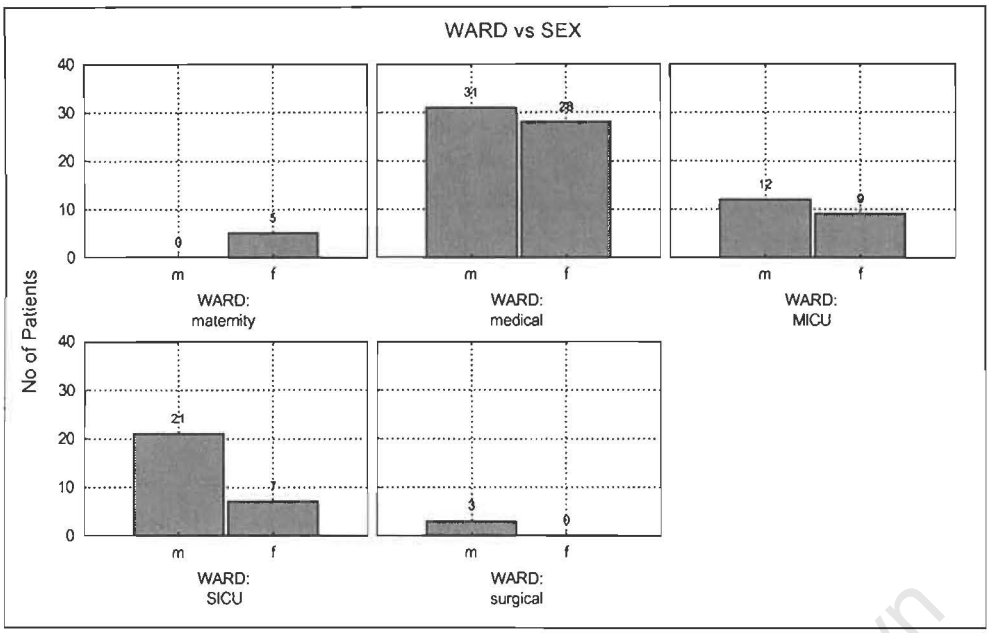


Figure 2

The sex and HIV status is demonstrated in figures 3 and 4. Of the HIV negative patients 62 were male and 41 female. All the HIV positive patients were black Africans (n = 12). This does not reflect the race distribution of the HIV negative patients (40 Black, 55 Coloured and 8 White) and is statistically significant ($p<0.001$). HIV status was not done in one patient. The majority of the HIV positive patients were female (8 female vs 4 male) although this did not reach statistical significance. Amongst the HIV positive patients there were three each with WHO stage 1, 2 and 3 disease and four with stage 4 disease. The mean CD_4 count ranged from 38 in the stage 4 patients to 328 with stage 1 disease.

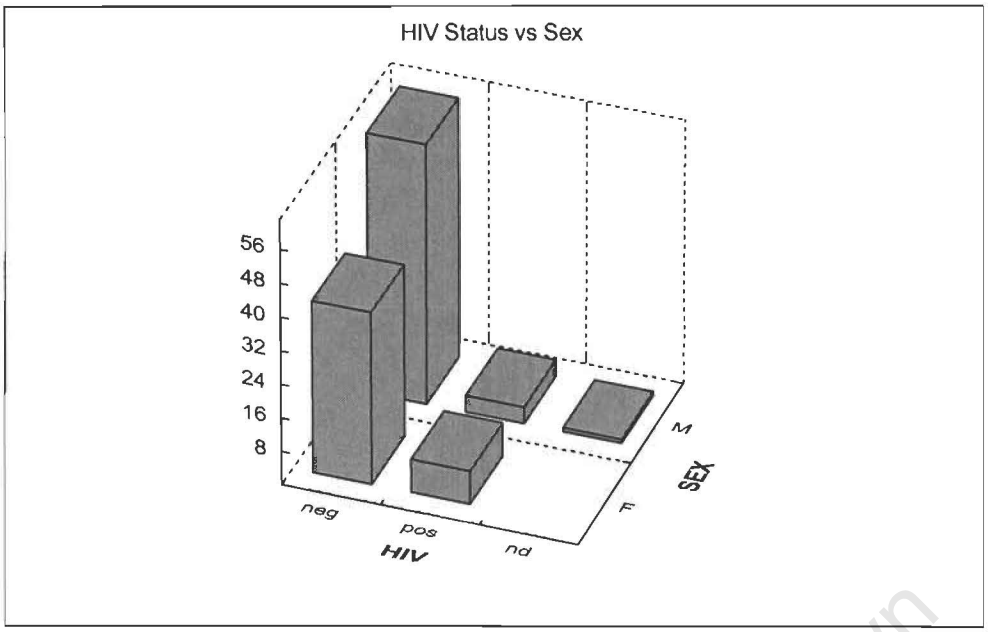


Figure 3

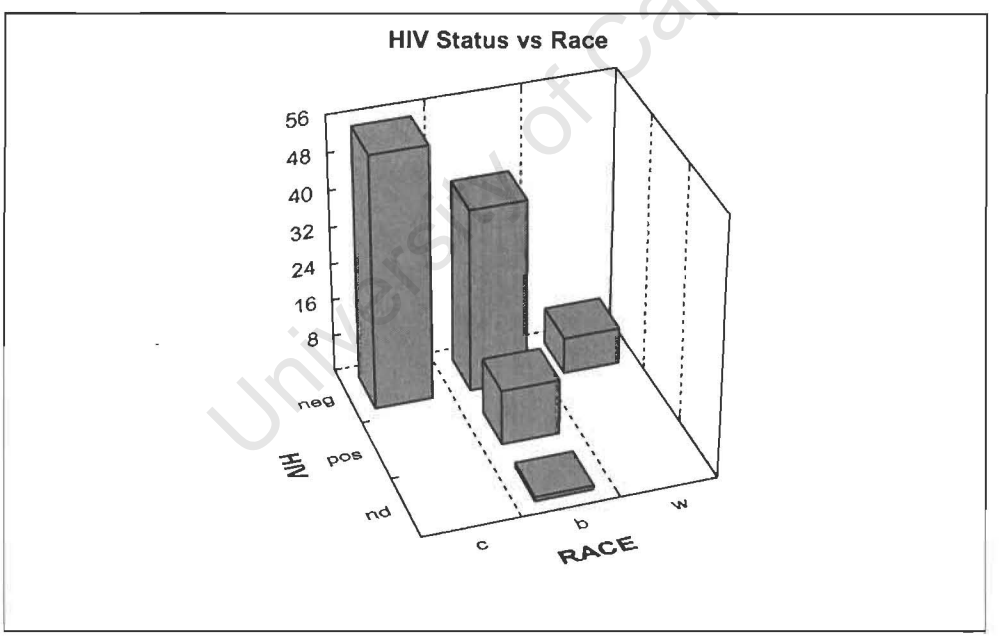


Figure 4

Four patients were Hepatitis B surface antigen (HepBsAg) positive. These patients were dialysed in a Hepatitis B isolation unit. One patient was not tested. This patient

presented as an emergency after hours. He was dialysed as if he was HepBsAg positive. Despite dialysis he died within twenty-four hours of admission.

Patients were assessed as to which discipline they were admitted under: (internal) medicine, surgery or obstetrics and whether they were admitted to a general ward or an intensive care unit (ICU). There were five maternity patients, 80 general medical and 31 surgical patients. Of these 2, 21 and 28 patients were in ICU's respectively.

Renal ultrasound was done in 71 of the patients. In 45 of the patients it was not done. Three of these patients were maternity and three were medical patients. The rest of these patients were ICU patients. One of the medical patients had had a renal US/S at a referring hospital but the full report was unavailable. In all 45 of these patients a clinical diagnosis of acute tubular necrosis had been made. In the patients who underwent renal US/S there were two patients with a single kidney demonstrated. In both cases this was due to a previous nephrectomy (trauma and renal carcinoma). There was one case of obstruction with hydronephrosis demonstrated. This was one of the patients who had a single kidney.

The mean starting blood urea was 43.8 +/- 22.3mmol/l and the mean creatinine was 966 +/- 645 μmol/l with a median starting creatinine of 768 μmol/l. The mean end urea, at death or one month after the last dialysis session, was 27.6 +/- 14.9mmol/l and creatinine 604 +/- 439 μmol/l with a median of 503μmol/l.

Eighty-eight percent (102) of the patients received intermittent haemodialysis (IHD). The remaining twelve percent received either continuous renal replacement therapy

(CRRT) or a combination of both CRRT and IHD. All of the CRRT patients were in intensive care units. They were haemodynamically unstable or in liver failure.

The majority of patients received five or fewer dialysis sessions with almost 85% of patients receiving ten or less (Figure 5). Only three patients received more than twenty sessions. One patient was dialysed 22 times and the other thirty. In both of these patients treatment was eventually withdrawn and the patient died. The last patient was treated with CRRT for two days and then 20 IHD sessions and made a complete recovery.

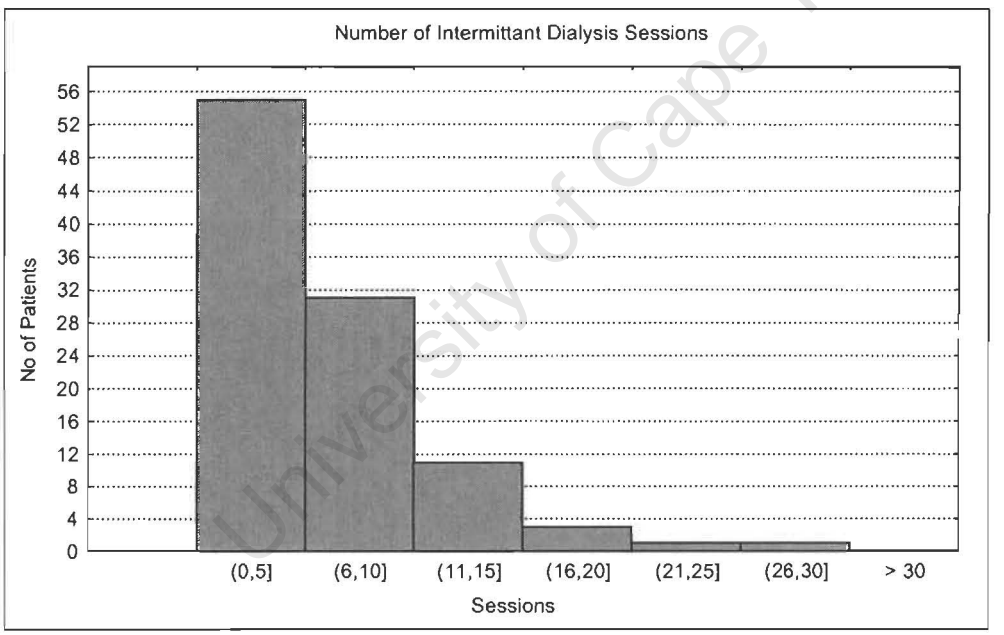


Figure 5

The haematology parameters: haemoglobin (Hb), white cell count (WCC) and platelets (Plts) of each patient were recorded. The Hb was 9 +/- 2.3 g/dl, the WCC 14,5 +/- 8.4 x 10^6 and Plts 228.5 +/- 167.9 x 10^9.

Every patient was clinically assessed by a nephrologist on at least one occasion. A clinical diagnosis as to the cause of the renal failure was recorded (Figure 6). Sixty eight percent of patients were assessed as having ATN. In twenty patients this was in addition to another diagnosis. Other diagnoses were chronic renal failure in six patients, acute interstitial nephritis in three, glomerulonephritis in four and chronic tubulointerstitial nephritis in two. Transplant rejection, obstruction, diabetic nephropathy, and chronic hypertensive nephrosclerosis were the concomitant diagnoses in one patient each.

Six patients presented for the first time with end stage chronic renal failure and were dialysed acutely whilst being assessed for the long-term dialysis and transplantation programme. Four of these patients had renal biopsies. Nine (8%) patients presented with malignant hypertension, requiring dialysis. Ten patients presented with miscellaneous causes of renal failure, including haemolytic uraemic syndrome (HUS), amyloid, bacterial pyelonephritis and microsporidiosis.

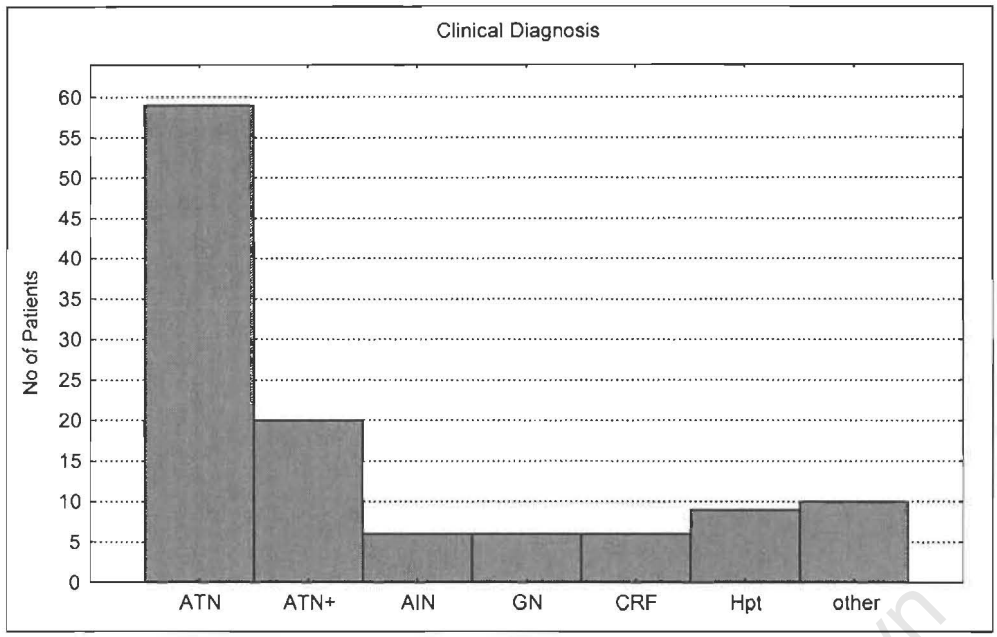


Figure 6

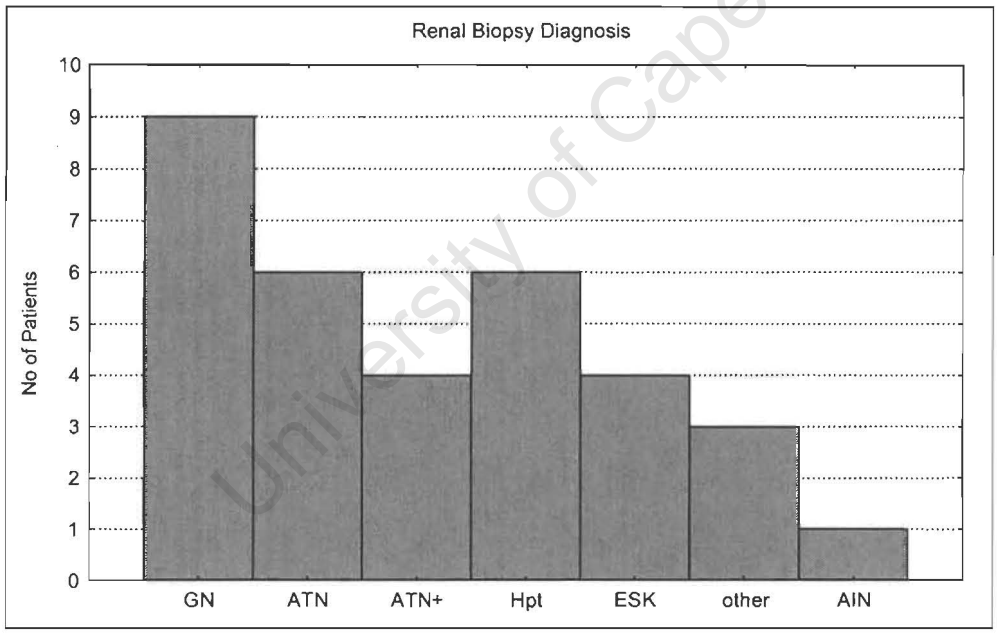


Figure 7

Thirty-two patients underwent renal biopsy (Figure 7). One of these patients was biopsied at the referring hospital and the biopsy was reviewed by our pathologists. Four biopsies showed end stage kidney (ESK). These patients all presented with an acute history of deteriorating renal function. Three patients had normal to large

kidneys on US/S and the fourth had 9.1cm kidneys with a well-preserved haemoglobin. Three showed evidence of underlying pathology: DM, FSGS and malignant hypertension. Ten biopsies showed an underlying glomerulonephritis. Five patients had a crescentic nephritis: three of these were post-infectious (PIGN), one was Goodpasture's, and one was pauci-immune type. Two patients had membranous nephropathy, one associated with hypertension and the other with ATN. One patient each had PIGN, systemic lupus erythematosis (SLE) and focal segmental glomerulonephritis (FSGS). Four patients with ATN had another pathology. Two patients had chronic interstitial infiltrate in keeping with chronic renal failure/end stage kidney, one patient had acute interstitial nephritis (AIN) and the last a membranous GN. Only one of the HIV positive patients was biopsied and this showed renal microsporidiosis. There were six biopsies showing evidence of malignant hypertension.

Pre-existing medical conditions were recorded for each patient (Figure 8). Sixty-one patients were previously well. Four patients had an underlying malignancy: two with gastric carcinoma, one with colonic and one with renal carcinoma. Of the patients who had heart disease, one had a dilated cardiomyopathy, two had valvular and three had ischaemic heart disease. The 'other' patients included one renal transplant patient, one patient with vasculitis, two patients with interstitial lung disease and two with collagen vascular disease. Alcohol use was recorded where the patient consumed in excess of forty grams of alcohol per day.

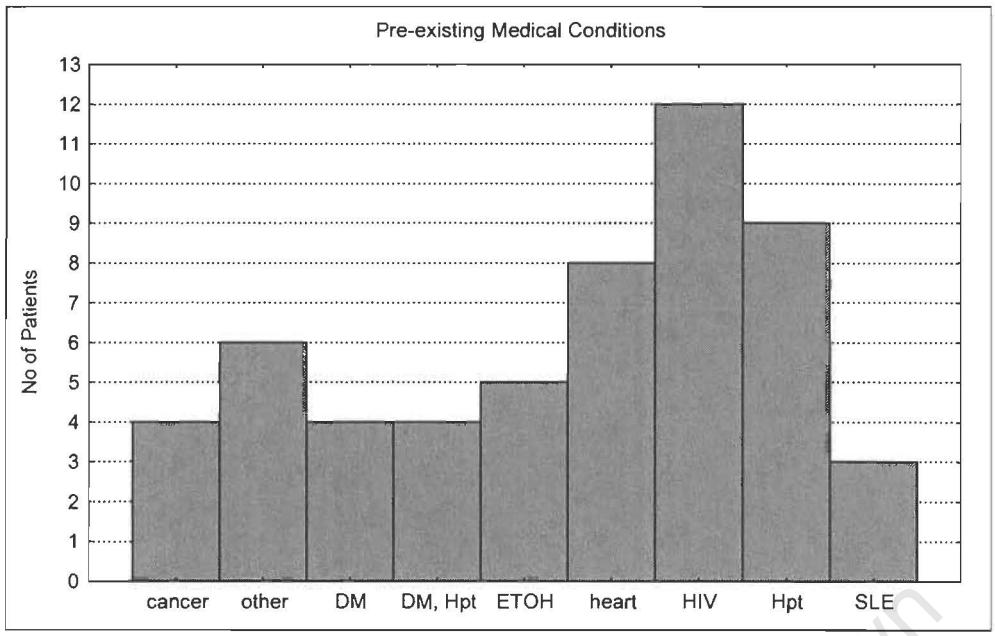


Figure 8 (ETOH: alcohol use, DM: diabetes mellitus, Hpt: hypertension)

A detailed drug history was obtained in every patient. This included questioning with regard to over the counter medications or medications received from traditional healers (traditional medication). In six patients a history of traditional medication use was obtained. Two of these patients underwent a renal biopsy. One patient had also used non-steroidal anti-inflammatory medications. This biopsy was in keeping with ATN. The other patient was on concomitant anti-tuberculosis medication. The biopsy showed ATN and AIN, which may have been due to the rifampicin. In five other patients medications were thought to play a role. Two patients who were septic and hypotensive were receiving gentamicin, one of whom was also receiving vancomycin. The aetiology of their renal failure was thought to be multifactorial. Three patients were on TB medication, one of these patients had a renal biopsy showing AIN.

The most life threatening indication for dialysis was recorded in each patient (Figure 9). In one patient the only indication was charcoal haemoperfusion for a drug

overdose. This patient is not reflected in the histogram. Forty-five percent of patients required dialysis for fluid overload with or without pulmonary oedema.

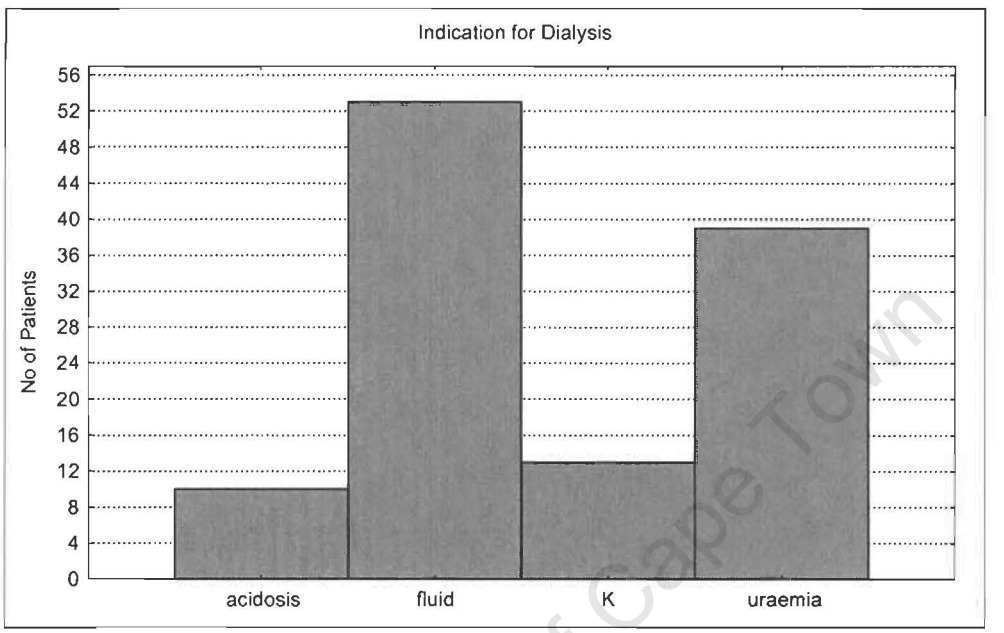


Figure 9 (K: hyperkalaemia, fluid: fluid overload)

One hundred and thirty femoral, twenty internal jugular and four subclavian lines were used. Complications arising from line insertion were monitored (Figure 10). All of these were secondary to femoral lines except for one case where an internal jugular line was incorrectly positioned. The 'other' category included two catheters where one of the ports clotted, one case of multiple (>3) passes prior to successful venous access with resultant haematoma, one instance where the guide wire was left in the femoral line and the last was the above mentioned complication of an internal jugular line. All complications were managed conservatively. This involved removal of the line, replacement at a distant site and the administration of antibiotics or

anticoagulation where indicated. There was no resultant mortality related to acute dialysis line placement.

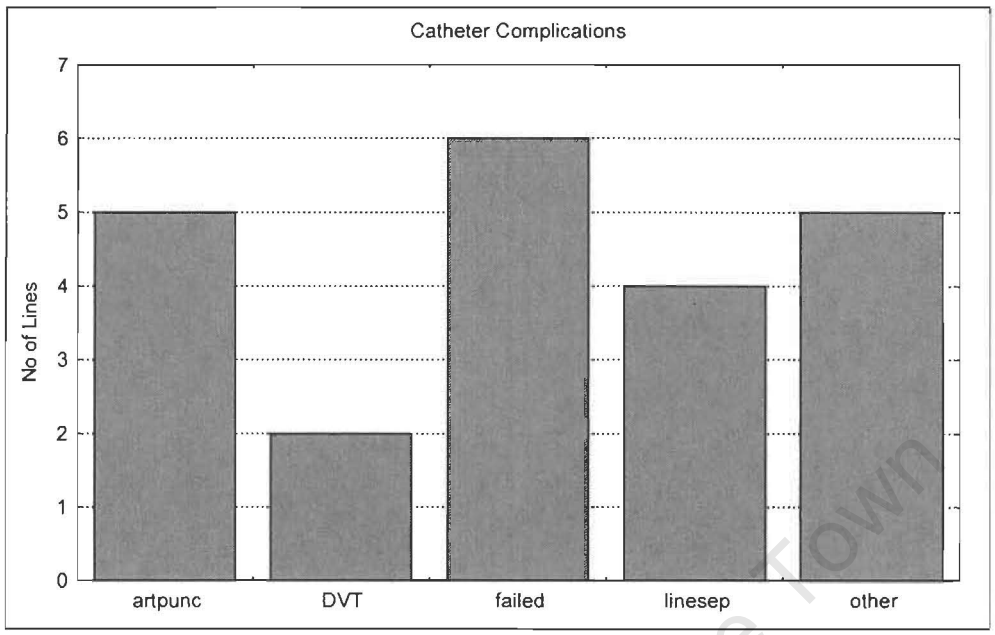


Figure 10 (artpunc: arterial puncture, DVT: deep vein thrombosis, linesep: line sepsis)

In sixteen patients treatment was withdrawn. Seven of these patients treatment was withdrawn as their general medical condition was deteriorating and the prognosis was assessed as being hopeless with two of these patients diagnosed with advanced malignancy. The remaining nine patients would have survived had they been offered long term dialysis. Due to the limited resources at Groote Schuur Hospital patients must meet strict medical and social criteria to be accepted onto RRP. Three of these patients were turned down because they were older than fifty. Four patients were sent home and no follow up is available, although it is presumed that they died. These patients have been excluded from subsequent analysis. The remaining twelve are included with those patients who died whilst still receiving treatment.

Overall 52.6% of the patients died (Figure 11). In sixteen of the patients there was no renal recovery and they were accepted onto the long term renal replacement programme (RRP). 36.6% (41) of the patients recovered.

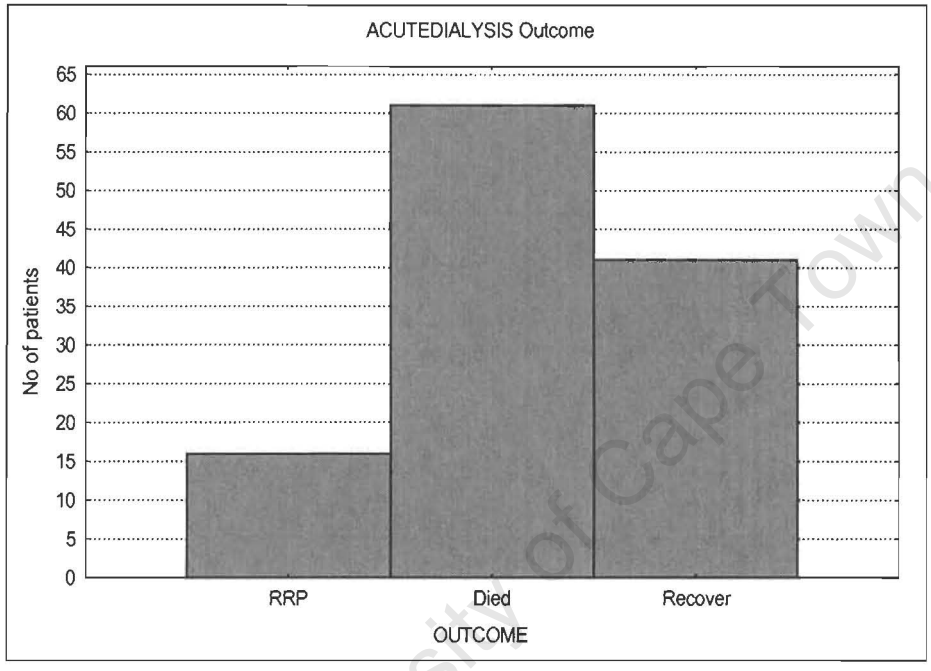


Figure 11

Of the patients who recovered fifteen (36.6%) had normal renal function as assessed by serum creatinine. Of the remaining twenty-six patients with abnormal renal function, follow up of at least one month was only available in twelve (29.3%). Fourteen (34%) of patients were lost to follow less than one month after their last dialysis session.

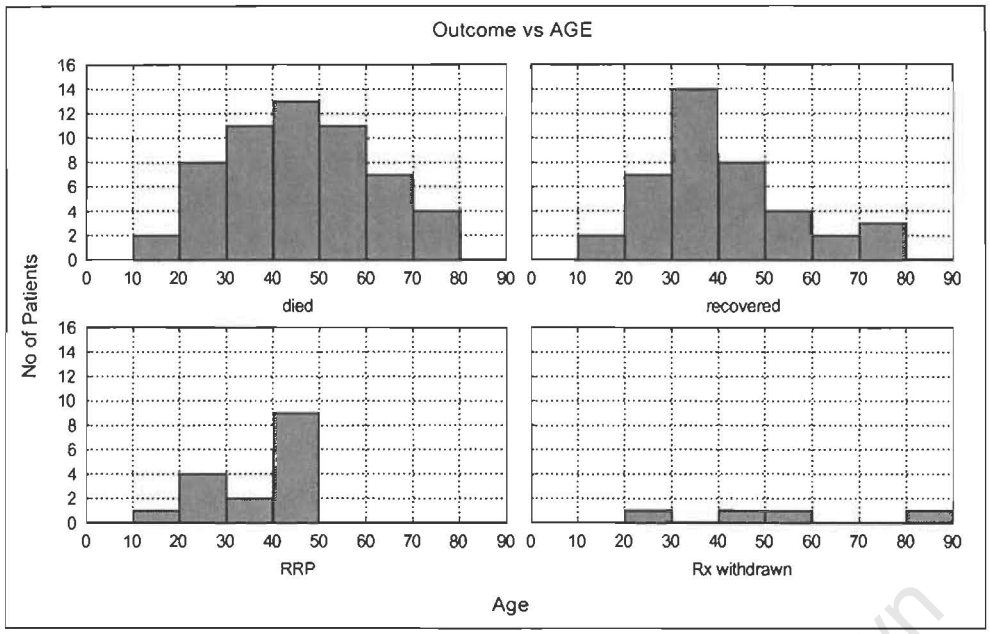


Figure 12

Age is a risk factor for patient survival. Those patients who died had a mean age of 46.4 +/- 15.6 and the survivors (recovered + RRP) 40.1+/- 13.6 (p = 0.02) (Figure 12). The difference in age of patients whose renal function recovered and those who either died or lived but required chronic dialysis (recovered vs. died + RRP) is however, not significant. There was no difference in outcome between the different race groups nor between male and female.

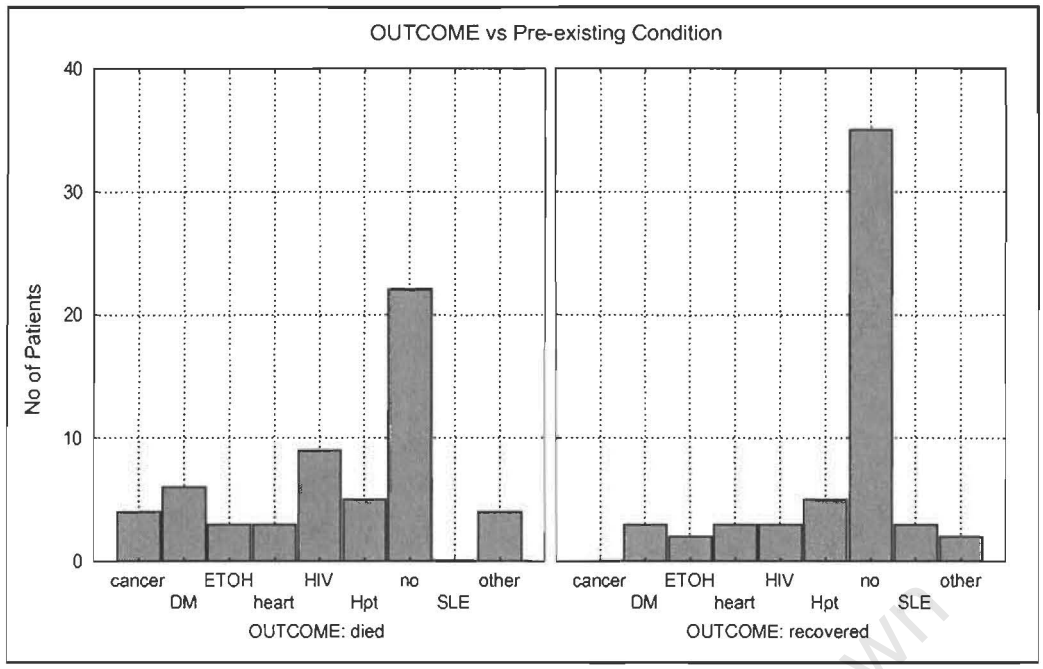


Figure 13 (No: previously well/no pre-existing condition)

When one looks at pre-existing medical conditions (Figure 13) there was not a significantly worse outcome associated with any one pre-existing condition and this held true for those patients with underlying malignancy or HIV infection. If all patients with pre-existing conditions are grouped together and compared with patients who were previously healthy (Figure 14) then there is a statistically significant worse outcome in patients with pre-existing medical conditions ($p = 0.01$).

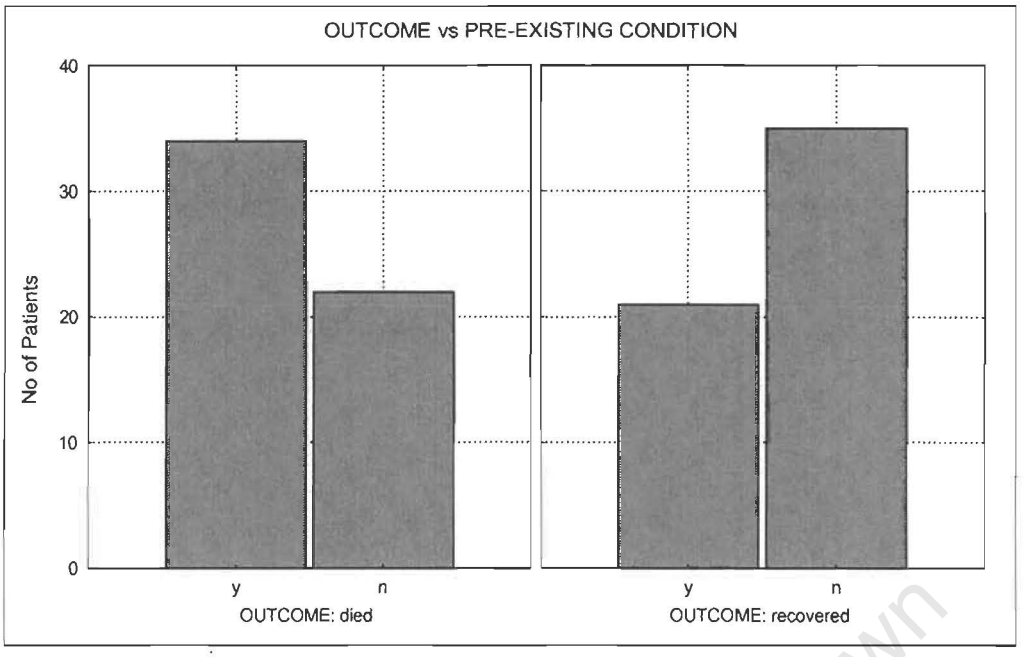


Figure 14 (y: pre-existing condition, n: previously well)

There was a trend to more medical patients dying as compared to either surgical or maternity. However, this did not reach statistical significance (Figure 15). A similar pattern resulted when the same groups were compared with respect to renal recovery. The maternity patients were significantly younger (P = 0.02) at 26.8 +/- 7.5yrs but there was no statistical difference between the medical (42.9 +/- 14.4yrs) and the surgical patients (46.8 +/- 15.5yrs).

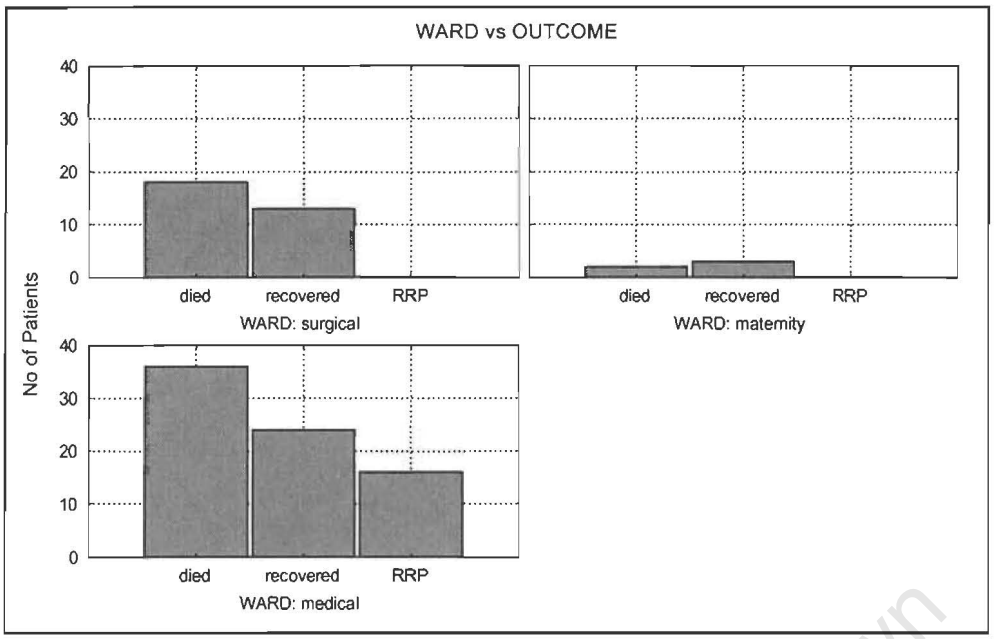


Figure 15

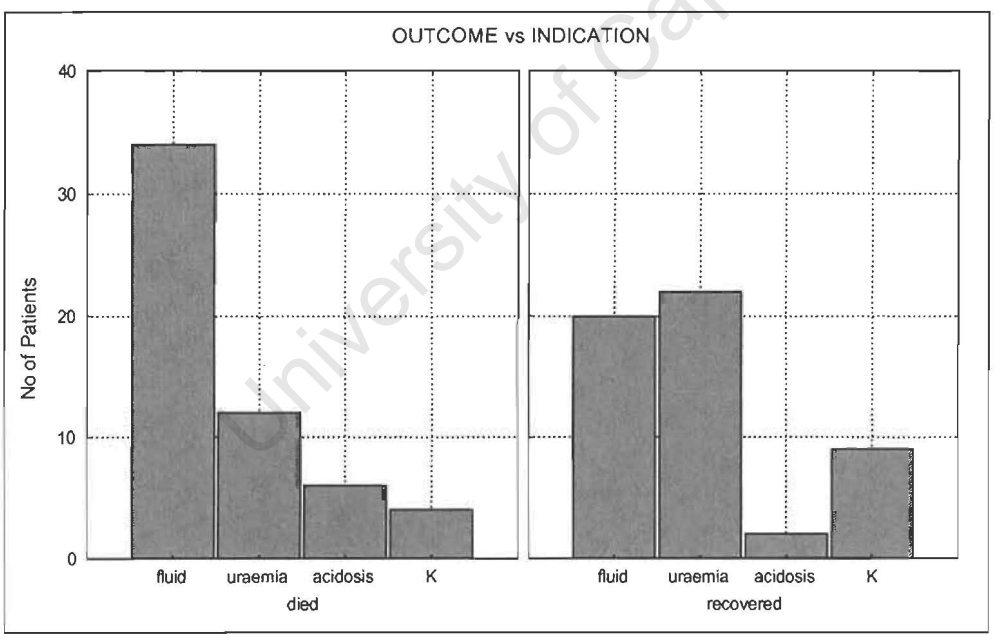


Figure 16

There was a trend for those patients who were dialysed for fluid overload to have a worse outcome, but this was not statistically significant (Figure 16).

Fourteen patients received CRRT. They were dialysed between four hours and twelve days. Six of the fourteen received a combination of both IHD and CRRT. All of these patients except one received CRRT initially, followed by IHD. Three of the fourteen patients survived. This was a statistically significant worse outcome than those patients who only received intermittent haemodialysis ($p = 0.01$). One of the three received two days of CRRT and no further renal support, the other two received prolonged renal support of 10 and 20 further intermittent dialysis sessions.

Discussion:

The renal unit at Groote Schuur Hospital is a tertiary referral centre in Cape Town. Many of the 116 patients who required dialysis were referred from secondary hospitals. This is particularly the case for the obstetric and medical patients. By international standards it is a busy unit (Ronco et al. 2001).

Demographics

Reports from the developed and the developing world suggest that the average age of patients admitted to hospital with acute renal failure is getting older. This is probably related to a smaller percentage of cases related to obstetric and surgical problems and increasing number of medical patients (Utas et al. 2000). The mean age of our patients was younger than that reported by Utas et al. This was despite having very few obstetric patients in our series. Both surgical and medical patients incorporated a younger group of patients than seen in other studies from developed countries (Turney et al. 1990) (Biesenbach et al. 1992). However this was similar to a local study published in Nephron (Seedat and Nathoo 1993). Two factors may go some way to explain this: firstly a high percentage (51.6%) of the surgical patients were trauma related. As noted in other studies these patients are significantly younger (Turney 1990). Secondly, amongst the medical patients there is an increasing incidence of HIV positive patients requiring dialysis.

HIV Positive Patients:

All the HIV positive patients were black Africans. In addition to this the majority were female. These demographics mirror those noted in a previous study done at this

hospital looking at renal biopsies in HIV positive patients (Twahir M, in press). This may to some extent be influenced by this hospital's drainage area and referring secondary hospitals, one of which drains a large lower socio-economic, predominantly black community. This group of patients had a high mortality (75%). The three patients who survived all had low CD4 counts (<100). Clinically they were WHO stage 1, 2 and 4. None of these three presented with sepsis. Two had severe, culture negative diarrhoea and the third a history of traditional medication ingestion, thought to have resulted in toxin induced ATN. Eight of the remaining nine patients presented with sepsis alone or complicating their presentation. They were dialysed for a similar number of dialysis sessions as those HIV positive patients who died: 2.3 vs 2.55. In HIV negative patients, both medical and surgical, sepsis is an independent risk factor for mortality (Turney 1990) (Biesenbach et al. 1992). Despite the small numbers in our study a univariate analysis of sepsis and outcome shows that this holds true in HIV positive patients too.

ARF Aetiology

The high proportion of ARF resulting from medical causes reflects that seen elsewhere in both the developed and developing world (Biesenbach et al. 1992; Prakash et al. 1995; Utas et al. 2000). Twenty eight of the thirty one surgical patients were in the SICU. Many high risk surgical patients were electively ventilated post-operatively. Also, in some cases, the reason for SICU referral was the development of ARF, with or without other organ failure.

In the study by Turney et al from England out of 1347 patients included in the study there were 11 patients (0.8%) over a thirty year period who presented with malignant

hypertension. It is noted that this disease has become uncommon. In South Africa the prevalence of hypertension in the urban population is 20 – 30% (Seedat and Nathoo 1993). What is surprising is that in the study from Natal, South Africa, there were no patients with documented malignant hypertension as a cause of ARF. Nine (7.7%) of our patients had hypertension, six of these patients had renal biopsy proven malignant hypertension. Although primary malignant phase hypertension is still found the incidence is decreasing (Milne 1998). The high incidence in our study may reflect the relatively poor primary health care services in the drainage area of our hospital.

A clinical diagnosis of chronic renal failure was made in six patients. They presented with advanced renal failure (mean urea: 80.2mmol/l), they however were not encephalopathic, with concomitant anaemia and renal size at the lower end of normal or small. None of these patients was biopsied. Four patients who presented with a clinical picture of ARF had evidence of end stage kidney on biopsy. We know from previous studies that the pre-biopsy diagnosis is correct in less than fifty percent of cases (Haas et al. 2000). Other studies on acute renal failure from the developing world do not make mention of this group of patients. This may just be a result of slightly different terms of reference for the study. Our study included all patients who were dialysed acutely in the one-year period, except transplant patients with delayed graft function.

Renal Biopsy:

Renal biopsy was undertaken in 32 patients. A careful clinical assessment, including laboratory results and radiology, was made in all patients. If the aetiology of the acute renal failure remained unexplained or in doubt a renal biopsy was performed. When

possible this was performed prior to the initiation of dialysis. All patients required optimal blood pressure control and normal bleeding profile prior to renal biopsy. Two patients underwent biopsy after not recovering from ATN. One of these patients the clinical diagnosis of ATN was confirmed and the other had a crescentic GN.

Ultrasound:

In our series renal US/S had a very low yield, with it changing our management in only one of the 71 patients scanned. It is, however, a non-invasive, cheap, and readily available investigation. In addition, it aided our diagnosis in several of the other patients, particularly in eight patients who had kidneys less than 8cm in size and other features of chronic renal failure.

Mode of Dialysis:

None of our patients received acute peritoneal dialysis. This is in contrast to another local study where peritoneal dialysis was the first line of dialysis (Seedat and Nathoo 1993). Other centres worldwide rarely use peritoneal dialysis (Ronco et al. 2001). The majority of our patients received intermittent haemodialysis. Our access to CRRT is very limited. At Groote Schuur Hospital we exclusively use continuous veno-venous haemodialysis (CVVHD). This is not only labour intensive but in our setting is also more expensive than IHD. Even for our acute HIV negative patients we practise dialyser reuse. This translates into IHD being significantly cheaper than CVVHD. CVVHD is reserved for patients who are haemodynamically unstable or in liver failure in addition to renal failure. The relative benefits of CRRT vs IHD are much debated in the literature. None of our patients was started on CRRT for extended indications in the absence of ARF. Although there is little evidence to support this

practise (Dunham 2001) it appears that it is in wide spread use throughout the world (Ronco et al. 2001). The significantly worse outcome of those patients receiving CRRT as opposed to IHD is therefore not surprising as they were the sicker patients.

Eighty-five percent of patients receiving IHD received less than eleven acute dialysis sessions with the majority being dialysed less than five times. This is in keeping with the findings of Biesenbach et al who noted that between 1985 and 1989 patients received a mean of six treatments with a range of 1 – 49. None of our patients received more than thirty acute dialysis sessions. Patients still dialysis dependent are reassessed six weeks after the last acute insult. A decision is made at this stage about acceptance on to the long term dialysis programme.

Although it was not recorded for each patient the vast majority of patients received acetate based dialysis, with only the occasional ICU patient receiving bicarbonate based dialysis.

Mortality:

The overall mortality of our patients was 52.6%. Renal survival was only 35% with 16 patients being accepted on to the long-term renal replacement programme. This mortality rate is similar to that reported elsewhere in the literature (Turney 1990) (Biesenbach et al. 1992).

In the study reported by Biesenbach G et al there has been a gradual improvement in mortality over a fifteen-year period. Surgical patients, however, still had a higher mortality than non-surgical patients. In our series there was a trend to more medical

patients dying as opposed to surgical. This did not reach statistical significance. It was, however, despite the medical patients being younger. This discrepancy may be accounted for by two factors. Firstly, all the HIV positive patients were medical and they had a high mortality (75%). This is in contrast to a study reported in the United States of America where the recovery from ARF in HIV positive patients was similar to HIV negative patients (Perazella 2000). Secondly, amongst the surgical group there was only a small percentage of post cardiac surgery patients. In overseas studies this group makes up to 35% of the surgical patients (Turney 1990). This group has been shown to have a high mortality (Groeneveld et al. 1991). Of the five post cardiac surgery patients in our study, four died. One of these patients had recovered renal function but on the day of discharge committed suicide.

In both local and international studies obstetric mortality is low. This is reported in the region of 15 – 25% (Turney 1990) (Seedat and Nathoo 1993). Our obstetric mortality was relatively high at 40%. We only dialysed five obstetric patients. One patient had acute on chronic renal failure. She developed cortical necrosis with no recovery of renal function. She was not a candidate for our renal replacement programme and treatment was withdrawn. The other patient developed pneumococcal pneumonia and died of multi-organ failure. We had no cases of acute renal failure complicating septic abortion. The incidence of ARF following septic abortion has declined dramatically over the last twenty years, especially since the liberalisation of the abortion laws in South Africa (Seedat and Nathoo 1993).

There have been suggestions in the literature that newer dialysis techniques and the use of bicarbonate based dialysis have contributed to the lower overall mortality

(Biesenbach et al. 1992). In our study these factors can not account for the comparable mortality that we achieved. Patient selection, younger age and improvements in overall care of patients in renal failure must therefore account for the acceptable mortality figures that we achieved.

Conclusion

Groote Schuur Hospital acute dialysis unit is a busy unit. Renal biopsy remains an important tool in the management of these patients and should be performed in all patients where there is doubt as to the cause of ARF and in those patients who fail to recover after a clinical diagnosis of ATN has been made.

We have been able to maintain a mortality rate, which is comparable to many units in the developed world. The challenge that lies ahead is to continue to improve the outcome despite continued limited resources that developing nations suffer. Most particularly will be the challenge of an ever increasing number of HIV positive patients who present to our institution with acute renal failure.

Appendix 1

ACUTE DIALYSIS SURVEY

PATIENT NAME: F/NUMBER:
DOB SEX RACE

DATE OF ADMISSION	
DATE OF 1ST DIALYSIS	
DATE OF LAST DIALYSIS	
HIV	
HEP B	
WHO stage	
CD4	
RENAL SIZE US/S	
START UREA	
START CREATININE	
END UREA	
END CREATININE	
NUMBER OF TIMES DIALYSED	
Hb	
WCC & LYMPHS	
Plts	

DIAGNOSIS RENAL: 1. 2. 3.

OTHER

DRUGS+/- TRAD. MED:

IV ACCESS FEMORAL R L

INT JUGULAR R L

CATHETER COMPLICATIONS

INDICATION FOR DIALYSIS: ACIDOSIS FLUID K^+ URAEMIA

RENAL BIOPSY

OUTCOME RECOVERY WITHDRAWAL DIED

RRP

Appendix 2

Abbreviations

5-HT	5-hydroxytryptamine
AIN	acute interstitial nephritis
ARF	acute renal failure
ATN	acute tubular necrosis
ATP	adenosine triphosphate
CRF	chronic renal failure
CRRT	continuous renal replacement therapy
DCT	distal convoluted tubule
DM	diabetes mellitus
DNA	deoxyribonucleic acid
DVT	deep vein thrombosis
EGF-1	epithelial growth factor - 1
eNOS	endothelial nitric oxide synthase
Erg-1	early growth response - 1
ERK	extracellular regulated kinase
ESK	end stage kidney
ETA	endothelin A
ETB	endothelin B
ETOH	ethanol
FSGS	focal segmental glomerulonephritis
GFR	glomerular filtration rate
GN	glomerulonephritis
Hb	haemoglobin
HD	haemodialysis
HepBsAg	Hepatitis B surface antigen
HGF	Hepatic growth factor
HIV	human immunodeficiency virus
Hpt	hypertension
HSP	heat shock protein
HUS	haemolytic uraemic syndrome
ICAM-1	Intercellular adhesion molecule 1
ICU	intensive care unit
IE	immediate early
IGF-1	insulin like growth factor - 1
IHD	intermittent haemodialysis
iNOS	inducible nitric oxide synthase
IV	intravenous
K	potassium
kDa	kiloDalton
KSP32	kidney specific protein of 32 kiloDalton size
LPS	lipopolysaccharide
MAPK	mitogen activated protein kinase
MCP-1	monocyte chemoattractant protein - 1

mRNA	messenger ribonucleic acid
MSH	melanocyte stimulating hormone
Na	sodium
NF-kB	Nuclear factor kappa B
NO	nitric oxide
PAF	platelet activating factor
PCT	proximal convoluted tubule
PIGN	post-infectious glomerulonephritis
Plts	platelets
RANTES	regulated on activation, normal T cell expressed and secreted
rh	recombinant human
ROS	reactive oxygen species
RRP	renal replacement program
Rx	treatment
S3	third segment
SAPK	stress activated protein kinase
SLE	systemic lupus erythematosis
tALH	thick ascending loop of Henle
TB	tuberculosis
TGF-B	transforming growth factor beta
TNF	tumour necrosis factor
WCC	white cell count
WHO	World Health Organisation

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