OUTCOMES OF RENAL TRANSPLANTATION IN PATIENTS WITH LUPUS NEPHRITIS: A SINGLE CENTRE STUDY IN CAPE TOWN

By

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Declaration

I Ahmed Khalifa Mohamed Almradi hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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After an intensive period of working, today is the day: writing this note of thanks is the finishing touch on my thesis. It has been a period of intense learning for me, not only in the scientific arena, but also on a personal level. Writing this thesis has had a big impact on me. I would like to reflect on the people who have supported and helped me so much throughout this period

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Figures and Tables

Chapter 1

Chapter 2

List of Abbreviations

ACE	Angiotensin-converting enzyme
ACR	Acute cellular rejection
AI	Activity Index
AMR	Antibody mediated rejection
aPL	Anti-phospholipid antibody
ATN	Acute tubular necrosis
ATG	Anti-thymocyte globulin
AVR	Acute vascular rejection
AZA	Azathioprine
B	Blacks
Bx	Biopsy
CAN	Chronic allograft nephropathy
CI	Chronicity Index
CCL2	Chemokine C-C Motif Ligand 2
C	Coloureds
CNI	Calcinuerin inhibitor toxicity
CKD	Chronic Kidney Disease
CCR2	C-C Chemokine Receptor Type 2
CyA	Cyclosporine A
CYC	Cyclophosphamide

F	Female
ESRD	End stage renal disease
GFR	Glomerular filtration rate
GN	Glomerulonephritis
HCV	Hepatitis C virus
HLA	Human Lymphocyte antigen
HTN	Hypertension
IFN	Interferon
ISN	International Society of Nephrology
LN	Lupus nephritis
LRD	Living related donor
M	Male
MMF	Mycophenolate mofetil
N/A	Not applicable
N	No
PRA	Panel reactive antibody
RAAS	Reninangiotensin aldosterone system
RPS	Renal Pathology Society
Scr	Serum creatinine
SLE	Systemic lupus erythematosus
SLICC	Systemic Lupus International Collaborating Clinics Classification

Tacro	Tacrolimus
TLR	Toll Like Receptor
Tx	Transplantation
W	Whites
Y	Yes

Abstract:

Background:Kidney disease (lupus nephritis [LN]) constitutes a feature of systemic lupus erythematosus (SLE) in up to 50 - 70% of patients with the disease. Although most LN patients are suitable for renal transplantation when they develop end stage renal disease (ESRD), the risk of recurrence of LN post-transplantation can be as high as 30%. Since the outcomes of renal transplantation in ESRD-LN patients has not been adequately studied in South Africa, the present study aims to retrospectively explore the aforementioned objective in a single centre.

Methodology: The study was designed as a retrospective descriptive study of patients with LN transplanted in the renal unit of Groote Schuur Hospital, Cape Town from 1stJanuary 2004 to 31stDecember 2013.

Results: There were 454 patients who were transplanted in the study period of which 15/454 (3.3%) had LN. The M:F ratio of LN patients was 1:14, mean age was 25±10 years, all were known with class- IV LN and 10/15 (66.7%) received graft from a cadaveric donor. Immunosuppression was initiated in 7/15 (46.7%) with combination of cyclosporine and azathioprine; in 2/15 (13.3%) with tacrolimus and azathioprine and in 6/15 (40.0%) with Tacrolimus and MMF. All patients received corticosteroids. Recurrence of LN was seen in one patient (6.7%) who developed class V LN. Graft rejection was diagnosed in 10/15 cases (66.7%) with types of rejection noted to be acute cellular rejection in 6/15 (40%), antibody mediated rejection 1/15 (6.7%) and chronic rejection in 3/15 (20%). ESRD occurred in 3 patients (20%) with causes from antibody mediated rejection (6.7%), chronic allograft nephropathy (6.7%) and renal artery thrombosis (6.7%). Mean time to ESRD was 16.0 months. Five deaths (33.3%) occurred from sepsis in 3/15 (20%), pulmonary embolism; 1/15 (6.7%) and progressive

ESRD after non-acceptance to the chronic dialysis program; 1/15 (6.7%). Mean time to death was 44.1 months.

Conclusion: This study shows that recurrence of LN in the graft kidney is uncommon in South Africa. However, effort to reduce high rates of rejection and improve graft and patient survival still needs to be studied.

Chapter 1: Literature Review

Background:

Systemic lupus erythematosus (SLE), commonly known as Lupus, is an autoimmune connective-tissue disorder with a wide range of systemic involvement (1). Various mechanisms have been proposed in the stimulation of autoantibodies production against ubiquitous self-antigens, including abnormal clearance of apoptotic material (2). While there are considerable variations in disease incidence, differences in disease prognosis and activity exists based upon the race and ethnicity.Renal involvement known as Lupus nephritis (LN) continues to be the major cause of morbidity and mortality in SLE patients (3-7). Approximately 10% of patients with SLE, willin due course develop end-stage renal disease (ESRD) or undergo renal transplantation as a treatment option(8).

The kidney is the most commonly involved visceral organ in SLE as urinalysis of asymptomatic patients often shows hematuria and proteinuria and 50% of patients could also develop overt abnormal renal function (9-10). SLE affects people from every part of the world and has been shown to be about nine times as common in females as in males. Furthermore, the cumulative incidence of LN has been reported to be higher in Asians (55%), patients of black African descent (51%) and Hispanics (43%) in comparison to Caucasians (14%) (11-16).

The aim of this study is to document the outcome of ESRD patients with LN who received a kidney transplant at a single centre in Cape Town. There are no reports of outcome studies on LN patients who have been transplanted from South Africa. Although this study is focused on the outcome of kidney transplanted patients with LN, it is relevant to present some context by providing a brief overview of the pathogenesis, classification, diagnosis and treatment approaches to LN in order to maximize our understanding of the outcomes of renal transplant patients with LN.

Pathogenesis of LN

The pathogenesis of LN involves various extra-renal and intra-renal pathogenic mechanisms. While extra-renal mechanisms involves immune intolerance to nuclear autoantigens, clinically detected as antinuclear antibodies and exacerbatedInterferon-

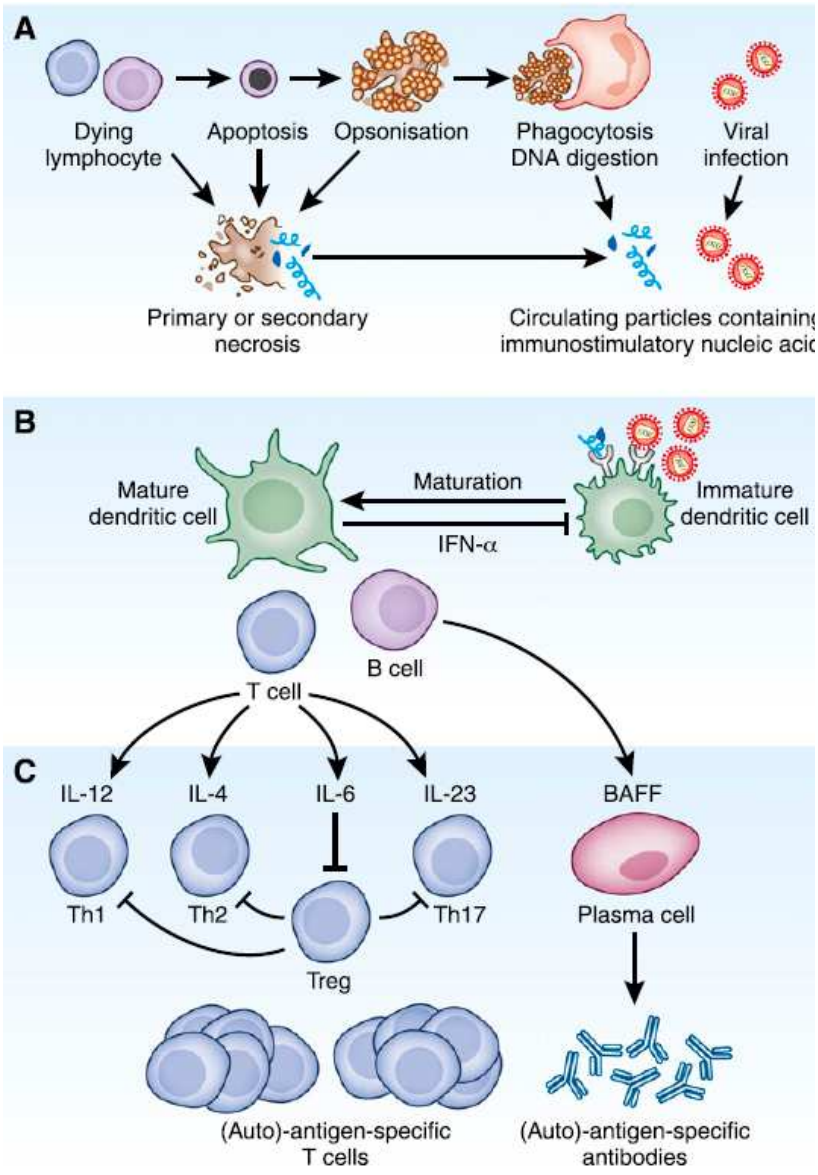
alpha(IFN-α)signalling, dendritic cells, T helper cells, B cells and plasma cells response, the intra-renal aetiology involves antibody binding to multiple intra-renal autoantigens, tertiary lymphoid tissue formation, localized antibody production and intra-renal complement activation (17).

Extra-Renal Pathogenic Pathways

SLE involves compromised cell death mechanisms such as mutations in apoptosis and delayed apoptotic cell clearance through opsonisation by complement proteins and their removal by phagocytosis (18-19). The delay in clearance of apoptotic cells leads to the incomplete degeneration of nuclear components by the immune system thereby stimulating production of anti-nuclear antibodies (20). Further, this pseudo anti-viral immune mechanism also triggers the antigen presenting cells, specifically dendritic and B cells which secretes large amount of type I IFNs exaggerating the anti-viral immune response. In-extension, hyper stimulation of antigen presenting cells results in the aberrant proliferation of B and T lymphocytes which turns to be autoreactive lymphocytes producing several autoantibodies in SLE (21) (Figure 1).

Several environmental factors have been reported to trigger SLE activity. While viral infections stimulate release of IFN-alpha thereby triggering antiviral immunity and lupus disease activity, bacterial infections stimulate nonspecific immune response involving a transient production of autoreactive lymphocyte clones (22). Additionally, bacterial products stimulate intra-renal immune cells and renal cells with consequent exacerbation of proteinuria and kidney damage. Ultraviolet light also act as an environmental trigger of SLE activity by enhancing the number of apoptotic cells due to keratinocytes cell death (23). Intake of certain drugs can also act as SLE inducer by inhibiting methyl-transferases resulting in the unmasking of endogenous nucleic acids and up-regulation ofToll Like Receptor7and 9(TLR7,TLR9) (24, 25). Hormones like, progesterone and estrogens also triggers the sex hormone-dependent immune-regulatory mechanisms (26).

Figure 1: Extra-renal pathogenic mechanisms of LN (From Lech & Anders, J Am SocNephrol 24: 1357–1366, 2013)



A) Cell Death and Dead Cell Mechanisms B) Induction of Anti-viral Immunity C) Aberrant Lymphocyte Proliferation

Intra-Renal Pathogenic Pathways

Among the several intra-renal mechanisms, immune complex-mediated renal damage is reported to play considerable role in LN. Studies have shown that circulating immune complexes passively deposit in the mesangium, sub endothelial, sub epithelial spaces or in peritubular capillaries giving rise to class I and II lesions, class III and IV lesions, class V lesions, and overlapping III/IV and IV/V lesions respectively depending on the severity of LN (27,28). However, the disease development is not restricted to the deposition of circulating immune complexes as various studies expressed the formation of *in situ* immune complexes within the glomerulus due to the secondary binding of nucleosomes generated from renal cells with circulating antibodies (29). Further, these intrarenal immune complexes activate the complement system which is genetically compromised in SLE patients, complement stimulate immune complex–related renal inflammation, overalldeposition of sub-epithelial immune complexes results in secondary membranous GN and nephrotic syndrome by damaging podocytes(30,31,32).

In-addition, circulating immune complexes triggers intrarenal inflammation through TLRs present in macrophages and dendritic cells which in turn produce significant amount of pro-inflammatory cytokines, IFN-alpha and IFN-beta (33-35). activated IFN signalling further attributes to renal damage by triggering the formation of tubuloreticular structures or inclusions, one of the hallmarks of LN (36, 39).

LN is characterised by the invasion of Cytotoxic T cells, Th17 T cells, as well as B cells (40). Different chemokine family members like CCL2, place CCR2+ proinflammatory macrophages and T cells into the glomerulus and tubulointerstitium (41,42). These infiltrating leukocytes were reported to form *de novo* perivascular tertiary lymphoid organs inside the kidney, which provide environment for clonal expansion, proliferation and activation of B cells in proximity to T cell aggregates (43).The proliferating B cells produces local inflammation, tissue pathology and autoantibody production (44,45,46). However, the body's immune system initiates healing response against immune

complex mediated renal damage which further exacerbates the renal pathology. It is reported that the healing response initiates focal tuft necrosis followed by the deposition of extracellular matrix over migrating parietal epithelial cells in the glomerular tuft and Bowman's space resulting in global glomerulosclerosis, also referred to as class VI LN (47).

Diagnosis and Classification of LN

According to the Systemic Lupus International Collaborating Clinics Classification (SLICC) criteria, LN is clinically diagnosed when a patient with SLE showed persistent proteinuria (>0.5 g/24 h) or cellular red cell casts (48). Further, Lupus Nephritis has also been classified based on the histological features assessed in renal biopsy, as per the standards established by the International Society of Nephrology (ISN) and Renal Pathology Society (RPS) in 2003 (49). The main histological manifestation of LN is immune complex mediated glomerulonephritis which manifests clinically as asymptomatic proteinuria, hypertension, microscopic hematuria, active urinary sediments, nephritic syndrome, and progressive renal failure (15,16).Based on the glomerular pathology, ISN/RPS system has classified LN in 2003 as indicated in Table 1 (49).

Table 1: Classification of Lupus Nephritis as per ISN/RPS, 2003.

Disease class	Description
Class I	Minimal mesangial lupus glomerulonephritis (LGN)
Class II	Mesangial proliferative LGN
Class III	Focal LGN (<50% of the total number of glomeruli):
	III (A) Purely active: focal proliferative LGN
	III (A/C) Active and chronic
	III (C) Chronic: focal sclerosing LGN
Class IV	Diffuse segmental (IV-S) or global (IV-G) LGN (50% or more of the total number of glomeruli):

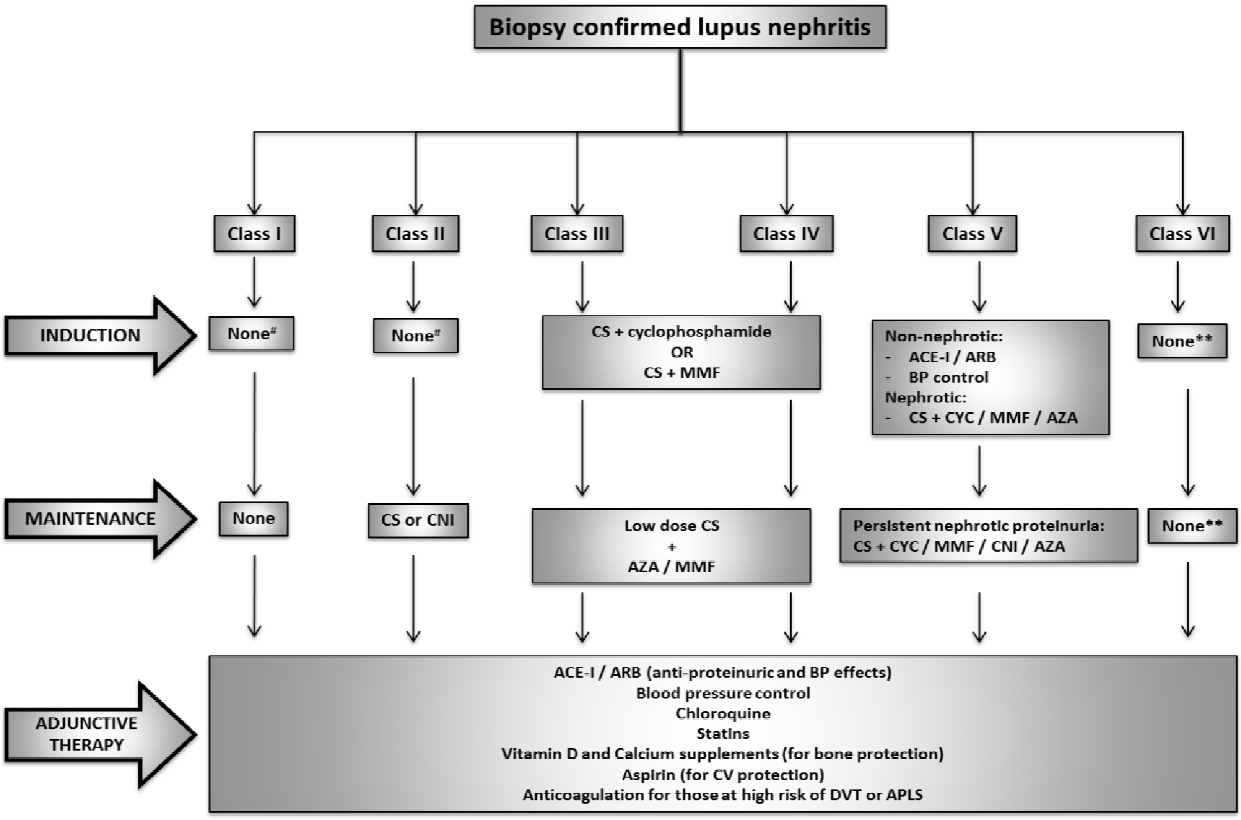
	IV-S (A) or IV-G (A): diffuse segmental or global proliferative LGN IV-S (A/C) or IV-G (A/C)
	IV-S (C) or IV-G (C): diffuse segmental or global sclerosing LGN
Class V	Membranous LGN
Class VI	Advanced sclerotic LGN (>90% of glomeruli globally sclerosed without residual activity): end stage LGN

Class II and Class V patients have a weak response to renal function over long time periods under observation (50). However, patients with Class III and Class IV have more serious disease progression. Proliferative form of LN, which include class III, class IV and mixed class V occur more as compared to other forms.Moreover, renal biopsies were scored for their activity and chronicity implicating reversible or irreversible lesions respectively. The activity index (AI) was scored at the scale of 0 to 24 obtained as the sum of six histologic features-endocapillary proliferation, infiltration of glomerular leukocytes, wire loop deposits, fibrinoid necrosis, and karyorrhexis, cellular crescents and interstitial inflammation, each of which can be individually scored as 0 to 3+. Similarly, chronicity index (CI) was score at the scale of 0 to 12, obtained as the sum of glomerulosclerosis, fibrous crescents, tubular atrophy, and interstitial fibrosis, each of which can be individually scored as 0 to 3+. An AI >7 and CI>3 indicates poor long term outcomes in lupus nephritis (28,51,52,53,54).

Treatment

The treatment of LN broadly follows a bi-phasic patterni.e. induction and maintenance based on the histopathological grading of the disease as mentioned in Figure 2 (55).

Figure 2: Treatment strategies of patients with Lupus Nephritis (From Okpechi et al. SAMJ.2015Dec;105(12):1071)



APLS = antiphospholipid syndrome;AZA = azathioprine; ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CNI = calcineurin inhibitor; CS = corticosteroid; CYC = cyclophosphamide; DVT = deep-vein thrombosis; MMF = mycophenolate mofetil; CV = cardiovascular).

* Immunosuppression to be dictated by extrarenal manifestations.

† Patients should be prepared for renal replacement therapy (dialysis/ transplantation).

Treatment of ISN Class I and II LN

Usually patients with ISN class I and II LN did not seek renal directed therapy rather the clinical conditions can be maintained using conservative non-immunomodulatory therapeutics. Use of anti-hypertensive therapy like angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers has been recommended as the first-line of treatment (56). These drugs act upon renin angiotensin aldosterone system (RAAS) by decreasing intra-glomerular pressure, systemic arterial BP, urinary protein excretion, and delayed progression of chronic kidney disease to ESRD (57,58).

Induction therapy for Class III and IV LN:

Patients with Class III and IV LN were usually subjected to three consecutive pulses of intravenous methylprednisolone (500 – 750 mg daily) in association with immunosuppressive agents: cyclophosphamide (CYC) (daily oral or monthly intravenous pulse therapy) or mycophenolate mofetil (MMF). Continued treatment with oral prednisone (1mg/kg/day) after pulse treatment with methylprednisolone is recommended. In addition, other agents has also been explored in induction therapy regimen like Rituximab, an anti-CD20 monoclonal antibody that depletes B cells, calcineurin inhibitor with MMF or azathioprine plus corticosteroids, however these treatment strategies need extensive clinical trials (59, 60).

Maintenance and adjunctive therapy for proliferative LN:

In this phase, induction phase treatment is de-escalated in order to reduce the progression of chronic kidney disease. The main objectives of continued immunosuppressive therapy are to inhibit relapse and flares of disease activity leading to chronic irreversible renal scarring as well as to prevent chronic adverse effects of therapy. While immunosuppressive agents like MMF, azathioprine (AZA) and corticosteroids remains the ideal choice, calcineurin inhibitors are administered in special circumstances where patients exhibit intolerance to MMF and AZA or persistent heavy proteinuria (55).

Adjunctive therapies are commonly initiated at the Induction phase; however their continuation or discontinuation depends on the disease conditions. Several adjunctive therapies have been recommended in Lupus Nephritis treatment including RAAS inhibition for proteinuria and blood pressure treatment, osteoporosis treatment by calcium and vitamin D supplements, chloroquine, statins for hyperlipidemia treatment,

low-dose acetylsalicylic acid for antiphospholipid syndrome patients, anticoagulant for nephrotic syndrome patients and isoniazid for tuberculosis prophylaxis (55).

Treatment of ISN Class V LN:

MMF with or without calcineurin inhibitors has been reported to be potentially useful treatment for Class V LN. Other treatment options include oral cyclosporine or tacrolimus course, monthly intravenous pulses of cyclophosphamide, oral MMF, or oral azathioprine in combination with corticosteroids (55,61).

Treatment of Class VI LN:

Advanced LN is often recommended for renal replacement therapy like haemodialysis, peritoneal dialysis or transplantation.

Challenges in the Management of Lupus Nephritis

Some researchers shown that there are some negative misconceptions which can affect the treatment strategy for Lupus Nephritis. However, it has been suggested that the outcome of LN patients could be improved if these misconceptions are addressed, The following are ten common mistakes they have observed surrounding the management of patients with lupus nephritis, which seriously affect the lupus treatment (83).

1.Assuming intravenous cyclophosphamide as gold-standard for lupus nephritis induction therapy.

2.Inappropriate dosage regimen of corticosteroids.

3.Infrequent use of antimalarial agents.

4.Urinary sediment usage as response criteria.

5.Improper scaling of immunosuppression treatment intensity in class V membranous lupus and other classes of lupus nephritis.

6.Discontinued treatment by patients on treatment failure.

7.Inappropriateuse of immunosuppressive agents in patients with advanced kidney disease.

8.Avoiding monitoring of adverse effects of immunosuppressive agents and using prophylaxis.

9.Unnecessary biopsy undertaking from high-risk patients considering the patient's non-responsive for therapy at advanced stage.

10.Poor decision making regarding treatment in the pregnant lupus patient.

Lupus Nephritis: Data from South Africa

Data from South Africa shows that LN is the most frequent secondary glomerular disease (39.0%) and a common cause of the nephrotic range proteinuria (17.2%) (84). In a retrospective study conducted by Ayodele et al in 2013, 50% of LN patients developed ESRD in South Africa with survival rate of 54, 34 and 27 % at 5-, 10and 15-year respectively (85). A recent systematic review reported the disease and treatment outcomes in LN patients from studies conducted in Africa (86). The study highlighted a clear paucity of multicenter studies in South Africa pertaining to LN due to poor infrastructure, excessive procedural costs, lack of skilled nephrologists, and difficulties in performing diagnostic renal biopsies (86, 87, 88)

End Stage Renal Disease (ESRD) and kidney transplantation

According to the records of John Hopkins Lupus Cohort, approximately 15% patients of Systemic Lupus Erythematous (SLE) developed ESRD within ten years of disease tenure (62,63). Many SLE patients with ESRD have been observed to be much younger than

non-lupus ESRD patients, suggesting that they could be excellent candidatesfor renal transplant therapy (62,63). Studies have also shown that with the development of ESRD, the SLE disease symptoms become quiescent, however the exact relationship between the two largely remains misunderstood(64).

Prior to renal transplantation, ESRD-LN patients were subjected to dialysis (hemodialysis or peritoneal) and studies reported an overall good survival rate for at least five years (62,65,66). However, infections, cardiovascular disorders and history of anti-phospholipid antibody (aPL) syndrome continue to be life-threatening factors within three months of dialysis (67). Overall, the choice to undertake dialysis prior to kidney transplantation incur several benefits like suppression of any residual lupus activity, dormancy of disease symptoms, and recovery of renal functioning in patients with rapidly progressive glomerulonephritis due to LN(65,66,67).

Although renal transplantation is an accepted form of therapy for LN patients with ESRD, several critical issues arises perhaps due to the presence of extra-renal complications either because of disease or immunosuppressive therapy. Among several issues, the key concern is the recurrence of LN in the transplanted kidney. The incidence of recurrent LN in kidney transplant recipients has been reported to vary between 2-11%(68,69,70,71). Multiple studies identified a series of risk factors associated with the loss of allograft in lupus patients such as race (black African ancestry), gender (female), young age, presence of antiphospholipid autoantibodies, and kidney acceptance from living donors (72-76).

Kidney transplantation Outcomes in ESRD-LN patients

Renal transplantation in ESRD secondary to LN is believed to be associated with generally good outcomes, comparable with transplant outcomes in non-lupus ESRD patients. In a study by Stone et al, the allograft survival rate was found to be inferior in six out of ten cases in SLE patients when compared with comparison groups, while the remaining four cases expressed equivalent outcomes (77). Similar results were found in another study from University of Wisconsin while the study additionally found a better

survival allograft rate in transplant recipients from living donor than the cadaveric donor (78).The poor renal transplantation outcomes among SLE patients were largely attributed to the risk of recurrent lupus nephritis in the allograft and the presence of antiphospholipid autoantibodies (77).Table 2 demonstratesthe clinical outcomes of kidney transplants in patients with chronic kidney diseases secondary to LN, polycystic kidney disease and diabetes nephropathy (79).The study outcomes revealed equivalent graft and patient survival success rates in kidney transplant patients with end stage renal disease secondary to lupus nephritis and other kidney diseases. Further, the study results demonstrate substantially low occurrence of complication rate and risk of recurrence for lupus nephritis (79).

Table 2: Clinical outcomes of kidney transplants in patients with ESRD due to LN, and other kidney diseases(79).

Total Patients	Lupus Nephritis	Polycystic Kidney Disease	Diabetes Nephropathy
N=136	27 (19.9%)	31 (22.8%)	78 (57.4%)
Graft Survival			
1st Year	96.3%	90%	91.7%
3rd Year	82.5%	86%	80.3%
5th Year	82.5%	76.5%	67.9%
Rate of LN recurrence = 0.94%/person-year			

Better renal transplantation outcomes were reported in a single-centre cohort study that included 40 SLE renal transplantation patients.Graft failure was noticed in 30% cases due to allograft nephropathy, acute rejection, and humoral rejection mediated by positive anti-HCV antibodies and an overall patient survival rate of 91.4% was reported (80). Another single centre study from Brazil of 13 lupus renal transplant patients showed that the graft survival rates were 93.3%, 90.9%, and 85.7% at 1, 5 and 10 years,

respectively(81). One patient died with no occurrence of LN in any of the patients, suggesting renal transplantation as better alternative therapy in ESRD-LN patients (81).Finally, a study from the Gdansk Transplantation Centre demonstrated the survival rate of 89.4% (17 of 19) at ten years of follow up and showed that presence of antiphospholipid autoantibodies was a negative predictive factor of allograft survival (82).

Recurrence of lupus nephritis in the graft kidney

Reviews of published reports have shown a rate of clinically recurrent disease in the renal transplant of 2.0 to 9.0 percent in patients with lupus nephritis, which is thought to reflect diminished immunologic activity (94,72). The incidence of recurrent symptoms of systemic lupus was also low at 5.7 percent (94).

However, higher rates of recurrence of nephritis in the renal transplant have been reported in subsequent studies (76). In one study, of 44 patients with lupus, 41 underwent transplant renal biopsy, 3 was indicated and 38 were surveillance biopsies ; among those patient'srecurrent lupus nephritis was noted in 22, resulting in a recurrence rate of 54 percent. This higher incidence may be due to the increased use of allograft biopsies because the majority of cases were subclinical (76).

The frequency of recurrence was analyzed using data from the United Network for Organ Sharing files (72). Among 6850 kidney transplant patients with end-stage renal disease due to lupus nephritis, 167 (2.44 percent) had recurrence. Non-Hispanic blacks, females and younger recipients (33 years or younger) had increased odds for recurrence 1.88, 1.70 and 1.69, respectively(72).

Recurrence of lupus nephritis can occur as early as the first week to as late as 16 years after transplantation, with most occurring during the first 10 years (72).

Rationale for the current study

Being a developing country, patients in South Africa with irreversible renal failure have limited access to dialysis facilities due to socio-economic constrains unlike developed countries where access to treatment is readily available to ESRD patients. However, due to the presence of cadaveric donor transplant program in South Africa, renal transplantation is an affordable alternative option available to the ESRD patients, although a huge gap exists between the demand and availability of organs (89-93). Hence successful acceptance of allograft is of utmost importance in this part of the world. Although few studies have assessed the disease outcomes and prognosis in LN patients in South Africa, studies on outcomes of renal transplantation in LN patients from South African population is unavailable. The present study aims to investigate the outcomes of renal transplantation in a single centre retrospective study conducted at Groote Schuur Hospital, Cape Town from 1st January 2004 to 31st December 2013. It is hoped that the results of the present retrospective study will increase our understanding and improve the outcomes of renal transplant patients with LN in South Africa.

In the next chapter (chapter 2), I have provided in a journal ready manuscript format, results of the study conducted to assess patient outcomes. In that chapter, I discuss the demographic, clinical and key features ascribed to patient outcome.

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CHAPTER 2 – JOURNAL READY MANUSCRIPT

OUTCOME OF RENAL TRANSPLANTATION IN PATIENTS WITH LUPUS NEPHRITIS: A SINGLE CENTER STUDY IN CAPE TOWN.

Abstract:

*Background***:** Kidney disease (lupus nephritis [LN]) constitutes a feature of systemic lupus erythematosus (SLE) in up to 50 - 70% of patients with the disease. Although most LN patients are suitable for renal transplantation when they develop end stage renal disease (ESRD), the risk of recurrence of LN post-transplantation can be as high as 30%. Since the outcomes of renal transplantation in ESRD-LN patients has not been adequately studied in South Africa, the present study aims to retrospectively explore the aforementioned objective in a single centre.

Methodology: The study was designed as a retrospective descriptive study of patients with LN transplanted in the renal unit of Groote Schuur Hospital, Cape Town from 1stJanuary 2004 to 31stDecember 2013.

Results: There were 454 patients who were transplanted in the study period of which 15/454 (3.3%) had LN. The M:F ratio of LN patients was 1:14, mean age was 25±10 years, all were known with class- IV LN and 10/15 (66.7%) received graft from a cadaveric donor. Immunosuppression was initiated in 7/15 (46.7%) with combination of cyclosporine and azathioprine; in 2/15 (13.3%) with tacrolimus and azathioprine and in 6/15 (40.0%) with Tacrolimus and MMF. All patients received corticosteroids. Recurrence of LN was seen in one patient (6.7%) who developed class V LN. Graft rejection was diagnosed in 10/15 cases (66.7%) with types of rejection noted to be acute cellular rejection in 6/15 (40%), antibody mediated rejection 1/15 (6.7%) and chronic rejection in 3/15 (20%). ESRD occurred in 3 patients (20%) with causes from antibody mediated rejection (6.7%), chronic allograft nephropathy (6.7%) and renal artery thrombosis (6.7%). Mean time to ESRD was 16.0 months. Five deaths (33.3%) occurred from sepsis in 3/15 (20%), pulmonary embolism; 1/15 (6.7%) and progressive

ESRD after non-acceptance to the chronic dialysis program; 1/15 (6.7%). Mean time to death was 44.1 months.

Conclusion: This study shows that recurrence of LN in the graft kidney is uncommon in South Africa. However, effort to reduce high rates of rejection and improve graft and patient survival still needs to be studied.

Introduction

Lupus nephritis continues to be the most frequent cause of morbidity and mortality among patients with systemic lupus erythematosus (SLE) patients and approximately 40–70% SLE adults show clinical evidence of this renal pathology at presentation (1). Approximately 10 to 30 percent of patients with proliferative lupus nephritis progress to end-stage renal disease (ESRD), depending upon the disease severity, socioeconomic factors, level of treatment adherence, and response to initial treatment (2, 3). Although, an overall improvement in disease prognosis has been noticed in recent decades, report from the United States Renal Data System from 1995 to 2006 revealed an increase in the standardized incidence of ESRD due to lupus nephritis in younger individuals (i.e. Age <40 years) (4).

ESRD due to LN is not a contraindication to renal transplantation, however, extra-renal manifestations of SLE (such as multiple thrombosis from anti-phospholipid syndrome) or complications of treatment (such as severe opportunistic infections) may pose unique challenges. Several studies have reported on risk factors associated with allograft rejection in lupus patients including black non-Hispanic origin, female gender, young age, presence of anti-phospholipid autoantibodies, kidney acceptance from living donors and recurrence of LN in the transplanted kidney (5-9). The risk of recurrence of lupus nephritis (RLN) after transplantation may range between 2 and 30% (10). Data from the United State Network for Organ Sharing (UNOS) show that out of 6850 kidney transplant recipients, RLN was seen in 167 (2.4%) while 1770 (25.8%) experienced at least one episode of rejection (10).

Postransplant immunosuppression does not differ from that used routinely; the results of kidney transplantation largely depend on the clinical conditions at time of transplantation (1).Treatment with new and more potent immunosuppressive drugs may improve the outcome of these patients. Further, better survival benefit for ESRD-LN patients have been reported for hemodialysis and peritoneal dialysis subjected before renal transplantation.

There are currently no African data reporting on the outcome of kidney transplant patients with lupus nephritis. The aim of the present study is therefore to descriptively present the outcome of individual LN patients who were transplanted at Groote Schuur Hospital from 1st January 2004 to 31st December 2013. The study outcome was non-composite and defined as any of the following: occurrence of graft rejection, recurrence of LN in the graft, occurrence of ESRD or death of the patient even if with functioning graft.

Methods

Study Design:

This study was conducted as a retrospective descriptive study of patients, known with ESRD secondary to LN who underwent renal transplantation at Groote Schuur Hospital, Cape Town from 1st January 2004 to 31st December 2013. The study received ethics approval from the joint human research ethics committee of the University of Cape Town and Groote Schuur Hospital before commencement (UCT HREC # 033/2016).Patients' records were accessed from renal transplant unit database and data of transplanted patients with known SLE was selected for the study.

Data collection:

In this study, we collected data on the demographic and clinical features of patients including age, gender, date of birth, date of renal transplantation, date of last follow-up visit, class of lupus nephritis, type of renal transplant (cadaveric / living).We also collected data to assist with identifying patient outcomes includingoccurrence of

delayed graft function following transplant, any rejection post- transplant, serum creatinine (and eGFR) on day 1, 30, 90, 365 and last follow- up, immunosuppression regimen used (plus any changes during the post- transplant period), trough levels of the primary immunosuppression (high / normal / low), renal biopsy post-transplant, any recurrence of lupus nephritis, dialysis requirement and death.

Definitions:

-ESRD: End-stage renal disease after transplant will be defined as persistent lowering of GFR <15ml/min for more than 3 consecutive months whether dialysis requiring or not.

-Death: All-cause mortality in transplanted patients i.e any cause of death.

-Duration of follow –up: was defined as the difference between the date of last follow up and the date of renal transplant.

-Duration to ESRD(graft loss/failure): was defined as the difference in the date of occurrence of ESRD and date of renal transplant.

-Duration to death: was defined as the difference in the date of death and date of renal transplant.

-Graft rejection: determined only if a graft renal biopsy has been performed and shows evidence of cellular or antibody mediated rejection i.e acute or chronic rejection.

-Recurrence of LN: was defined as present only if a graft renal biopsy shows evidence of histological features of LN (i.e proliferative or non-proliferative types of LN with presence of mesangial, sub-epithelial or sub-endothelial immune deposits – IgG, IgM, IgA or C3)

Data analysis and Statistics:

Data analysis was performed with the objectives to a) assess the proportion of patients with graft rejection post-transplant, b) evaluate the proportion of patients who develop

recurrent lupus nephritis in the graft post-renal transplant, and c) determine the period prevalence of SLE transplants carried out at Groote Schuur Hospital, Cape Town for the study period. The data was analyzed with SPSS (version 22). Frequencies were described as percentages and time to death or ESRD was presented in months (median). Differences between groups (e.g. males and females or cadaveric and living) was additionally analyzed using students't-test and chi-square statistics.

Results

Demographic and transplantation characteristics

Table 1 provides a summary of the demonstrate the demographic features of the study cohort. There were 454 patients who were transplanted in the study period of which 15/454 (3.3%) had LN. Majority of the patients were females (14/15; 93.3%) with mean age at time of kidney transplantation of 25±10 years (Min-Max: 19.2 – 49.1 years). Also, there were 3/15 (20%) African and White patients, respectively with majority (60%) being coloured.

All 15 patients were diagnosed with class- IV LN and majority of patients received the transplant from a cadaver (66.7%).

Immunosuppressive Treatment Strategies

Table 2 provides summary of immunosuppressive agents used for each patient (initial and maintenance), HLA-PRA level at time of transplant and kidney function at day-1 and 1 year post-transplant. Twelve patients (11/15; 73.3%) had HLA-PRA level of 0%, 2 patients (13.3%) had PRA level <10% and another 2 patients (13.3%) had PRA level >10% but <20%. Only the 2 patients with PRA level >10% received induction therapy with anti-thymocyte globulin (ATG); all other patients received cyclosporine and methylprednisone (with or without Azathioprine as in initialtherapy). For maintenance therapy, most patients (7/15; 46.7%) received cyclosporine and Azathioprine; 13.3%

received Tacrolimus and Azathioprine and 40% received Tacrolimus and Mycophenolate mofetil.

Renal transplantation outcomes

The assessed outcomes identified in these patients have been summarized in Table 3: three patients (20%; #2, #5 and #7) had developed ESRD at the last date of assessment within a mean duration of 16 months from time of transplantations (min 15days – max 2years). All 3 post-transplant ESRD patients subsequently died during follow-up.One-year and 5-year graft survival was 93.3% and 80% respectively. Overall mortality in this cohort was 5/15 (33.3%) with cause of death identified as: sepsis in 3/5 (60%; #2; #3and #7), pulmonary embolism in 1/5 (20%; #14) and progressive ESRD after non-acceptance to dialysis (20%; #5).The mean time to death from transplantation was 44.1 months (min – max: 1.0 – 74.0) One patient (#14) died early (first month) following a massive pulmonary embolism.Eight patients (53.3%) experienced a form of graft rejection during follow up and were appropriately treated. Of those with rejection, 6/8 (75.0%) had acute cellular rejection; 1 patient (12.5%; #7) experienced severe acute vascular rejection with loss of graft within 15 days post-transplantand another patient had antibody mediated rejection (12.5%; #10). Graft biopsies performed at variable times (usually for worsening of serum creatinine) during follow up showed confirmed rejection in these patients and in 2 other patients (#8 and #14) showed calcineurin inhibitor toxicity and BK virus infection in one patient (#11). Chronic allograft nephropathy was eventually identified in 3 patients ((#3, #5 and #9).Only one patient (#13) had recurrence of lupus nephritis (class V) in the graft.

Discussion

Although systemic lupus erythematosus is common in South Africa and possibly a common cause of early chronic kidney disease, the contribution of lupus nephritis to the overall ESRD population may be small. However, given that patients with LN, are the

more likely of all CKD patients to be on chronic immunosuppression, it is important to assess the outcome of LN patients following a kidney transplantation. To the best of our knowledge, this study is the first in the African continent to assess and report the outcomes of patients with ESRD secondary to LN transplanted in a single centre in Cape Town.

The main findings of our study are: (i) increased mortality rate, particularly from sepsis, (ii) increased rejection rate and (iii) low recurrence of LN post-renal transplant. Patients with lupus nephritis may have received variable years and doses of various immunosuppression (particularly corticosteroids) before kidney transplant. Sepsis has been shown to be a common cause of death in LN patients related to cumulative dose of immunosuppression. Ayodele et al (from the same centre) in a retrospective outcome study of 105 patients with biopsy proven LN reported mortality in 32 patients (30.5%) with sepsis accounting for 37.5% of all mortality(26). Most patients in that study received cyclophosphamide and prednisone for induction and Azathioprine and prednisone for maintenancetherapy(26).Other authors have equally reported sepsis as major cause of mortality in LN patients as well as in renal transplant recipients(27-28-29). Many of the patients in our study had a low HLA-PRA prior to renal transplant and thus were not excessively immunosuppressed at time of transplantation. This shows that LN patients still have a high risk of sepsis-related mortality following renal transplant, likely from cumulative years of receiving immunosuppression pre-transplant. Increased monitoring for infections is therefore required in these patients and measures to ensure infection prevention and control (e.g. adequate vaccination or use of prophylaxis) need to be put in place. In comparison to similar studies, mortality in this study was found to be much higher as others have reported mortality well below 20% from non-African countries (Table 4).

In comparison to similar reports, we observed that graft rejection occurred quite frequently in our patients (53.3%) (Table 4). Golebiewska et al in a study from Poland reported occurrence of early acute rejection in33% of LN patients (compared to 21% others; p=0.16); acute rejection was also observed to be a predictor of graft loss at one

year post-kidney transplant (30).Although we didn't compare graft rejection rates in patients with LN compared to others in our study, it is still unclear why these patients had such a high frequency of acute rejection, especially as we can anecdotally report that medications adherence in our transplant clinics is very high.

It is noted that despite the high rates of renal involvement and relapse in native kidneys, recurrent LN in a kidney allograft is often infrequent and when it occurs is relatively benign, without significant effects on patient and graft survival(31). One study that reported a high frequency of recurrence (54%) found only class I and II LN(32). Golebiewska et al only reported one patient with recurrent LN in their cohort (30). Recurrence of LN in our cohort was quite low and only occurred in one patient who developed proteinuria and was found to have class V LN on repeat biopsy. This shows that recurrence of disease (LN) should not be a major concern when patients are being worked up for a kidney transplant as it has not been demonstrated to be related to associated with graft or patient loss.

The major limitations of the study are the retrospective design, heterogeneous characteristics of the recipients, low sample size andthus our inability to carry out survival analysis. Notwithstanding these limitations, this is the first study to report on the outcomes of transplanted patients with LN in the African setting and thus calls for further robust studies to improve our understanding of LN patient's outcome post-kidney transplant.

Conclusion:

This study shows that mortality in transplanted patients with LN is often due to infections and strategies to reduce the rate of sepsis in these patients need to be adequately addressed following kidney transplantation. We believe our findings provide further evidence that lupus is not a rare disease in South Africa, survival is not as good as in developed countries, recurrence of LN post transplantation is infrequent and causes of death are similar to those documented in other developing countries. Further studies are necessary to adequately characterize the outcome of these patients.

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Table 1:Demographic and clinical, andTransplantation characteristics in the cohort of SLETransplanted patients.

Patient number	Gender	Race	Year Tx	Age dx SLE	Age at ESRD	Interval SLE & ESRD	Age at Tx	Interval ESRD &Tx	Type Tx	LN class before Tx	Duration of follow up months
1	F	C	2004	32	37	5	40.8	3.8	Cadaveric	4	148
2	F	C	2004	14	23.1	9.1	27.1	4.1	Cadaveric	4	47
3	F	C	2004	33	36.3	3.3	36.1	0.7	Cadaveric	4	66
4	F	C	2004	31	33.1	2.1	33.11	0.1	LRD	4	140
5	F	W	2005	17	19.2	2.2	22	2.8	Cadaveric	4	27
6	F	C	2005	25	27.1	2.1	35.8	8.7	Cadaveric	4	125
7	F	C	2006	33	37.1	4.1	39.8	2.7	Cadaveric	4	74
8	M	W	2007	21	34.4	13.4	38.9	4.5	LRD	4	99
9	F	C	2007	28	34.6	6.6	43.4	8.8	Cadaveric	4	102
10	F	B	2009	22.2	23.4	1.2	27.2	3.8	Cadaveric	4	86
11	F	B	2009	14	16.5	2.5	19.2	2.7	LRD	4	13
12	F	C	2009	38	46.3	8.3	49.1	2.8	Cadaveric	4	77
13	F	C	2010	24	29.7	5.7	30.1	0.4	Cadaveric	4	67
14	F	W	2011	25	29.3	4.3	33.2	3.9	LRD	4	1
15	F	B	2013	23	24.3	1.3	25.2	0.9	LRD	4	31

F-Female; M-Male; C - Coloureds ; W – Whites; B – Blacks; SLE – systemic lupus reythematosus; ESRD – End-stage renal disease; Tx – Transplantation; LN – Lupus nephritis; LRD-living related donor.

Table 2: Combination of immunosuppressive drugs administered, HLA-immunological risk and Laboratory Data

Patient number	Gender	Race	Induction therapy	HLA-PRA level	SCr -1	eGFR-1	SCr-365	eGFR-365	Maintenance therapy			
									CyA+Aza	CyA+MMF	Tacro+AZA	Tacro+MMF
1	F	C	CyA + MP	0%	316	17	131	41	N	N	Y	N
2	F	C	CyA + MP	0%	376	17	170	35	Y	N	N	N
3	F	C	CyA + MP	0%	85	70	100	58	Y	N	N	N
4	F	C	CyA + MP	0%	110	52	142	39	Y	N	N	N
5	F	W	CyA + MP	0%	95	68	230	25	Y	N	N	N
6	F	C	CyA + MP	0%	318	15	114	50	Y	N	N	N
7	F	C	CyA + MP	0%	790	5	1057	4	Y	N	N	N
8	M	W	CyA + MP	5%	123	60	104	73	N	N	N	Y
9	F	C	CyA + MP + AZA	0%	484	10	141	38	N	N	Y	N
10	F	B	CyA + MP	0%	907	6	98	75	N	N	N	Y
11	F	B	CyA + MP	0%	226	31	120	60	N	N	N	Y
12	F	C	CyA+ MP + AZA	2%	526	8	85	65	Y	N	N	N
13	F	C	CyA + MP	0%	187	29	92	66	N	N	N	Y
14	F	W	ATG	14%	699	6	-	-	N	N	N	Y
15	F	B	ATG	11%	92	83	71	111	N	N	N	Y

F-Female; M-Male; C - Coloureds ; W – Whites; B – Blacks; CyA – Cyclosporin; MP – Methy prednisone; AZA – Azathioprine; ATG – Anti-thymocyte globulin; MMF – Mycophenolate mofetil; Tacro – Tacrolimus; HLA – Human lymphocyte antigen; PRA – Panel reactive antibody; Scr – Serum creatinine; eGFR – Glomerular filtration rate; Y-Yes; N-No

Table 3:Post-transplantation outcomes in study cohort

Patient_number	Gender	Race	Renal Bx post-transplant	Scr- last follow up visit	GFR- last follow up visit	Recurrance of LN	Post-Tx_ESRD	Interval to post-Tx ESRD (Yrs)	Death	Interval between TX and Death (months)	Type of Rejection
1	F	C	HTN	124	41	N/A	N/A	N/A	N/A	N/A	N/A
2	F	C	ACR	1168	5	N/A	Yes	1.92	Y	48.0	ACR
3	F	C	ATN / CAN	908	5	N/A	N/A	N/A	Y	66.0	N/A
4	F	C	ACR	141	37	N/A	N/A	N/A	N/A	N/A	ACR
5	F	W	CAN	807	6	N/A	Yes	2.0	Y	30.0	N/A
6	F	C	ATN	241	19	N/A	N/A	N/A	N/A	N/A	N/A
7	F	C	AVR	396	11	N/A	Yes	0.04 (15 days)	Y	74.0	AVR
8	M	W	CNI	169	38	N/A	N/A	N/A	N/A	N/A	N/A
9	F	C	Borderline ACR / CAN	95	54	N/A	N/A	N/A	N/A	N/A	ACR
10	F	B	ATN / AMR	102	54	N/A	N/A	N/A	N/A	N/A	AMR
11	F	B	BK Virus	130	50	N/A	N/A	N/A	N/A	N/A	ACR
12	F	C	N/A	82	67	N/A	N/A	N/A	N/A	N/A	N/A
13	F	C	ACR	119	45	Class V LN	N/A	N/A	N/A	N/A	ACR
14	F	W	CNI	193	26	N/A	N/A	N/A	Y	1.0	ACR
15	F	B	N/A	99	60	N/A	N/A	N/A	N/A	N/A	N/A

F-Female; M-Male; C - Coloureds ; W – Whites; B – Blacks; Bx: biopsy; Scr: serum creatinine; GFR: glomerular filtration rate; tx: transplant; LN: lupus nephritis; ESRD: end stage renal disease; F: female; M: male; C: coloured; W: white; B: black; ; ATN: acute tubular necrosis; HTN – Hypertension; ACR – Acute cellular rejection; CAN – Chronic allograft nephropathy; CNI – Calcinuerin inhibitor toxicity; AVR – acute vascular rejection; AMR – Antibody mediated rejection; N/A: Not applicable; Y: Yes;Tx – Transplantation.

Table 4: Comparison of selected lupus-related renal transplant outcome studies

Country	Author (Ref)	Year of publication	Sample size	Mean Age	Gender (% f)	Main donor type (%)	Post-Tx ESRD (%)	Rejection (%)	Mortality (%)
USA	Chelamcharla et al	2007	2886	36.3± 10.8	82	Cadaveric (66)	NR	34.9	58.4
Poland	Gołębiewska, et al	2016	19	40 ± 10	84.2	Cadaveric (94.7)	28.6	31.0	10.5
Spain	Cairoli et al	2014	40	36 ± 10.4	80	Cadaveric (58.0)	NR	30.0	8.6
Netherlands	Deegens et al	2003	23	34±12	91.3	Cadaveric (78.2)	4.3	32.0	14
Brazil	Oliveira et al.	2012	14	33±9	85.7	Cadaveric (67.0)	8.3	50.0	5.6
Iran	Ghafari et al	2008	23	22.45±16	78.3	LRD (100)	31	NR	17
South Africa	Almradi et al	2017	15	25±10	93.3	Cadaveric (66.7)	20.0	53.3	33.3

F-Female; Tx – Transplantation; LRD-living related donor;ESRD: end stage renal disease; NR: not reported; Ref-Reference;

Appendix 1: Data Capture sheet

patient_number

folder_number DOB Race year Tx

Date_dx_lupus Pre_tx_date_esrd

Date Tx Type Tx Lupus class before Tx

Scr -1		GFR-1	
SCr-30		GFR-30	
SCr-90		GFR-90	
SCr-365		GFR-365	

CyA+Aza		Cya+MMf		Tacro+MMf		Tacro_Aza		Siro+Aza		ATG I	

Was levels/ Th or Lw

Renal Bx post-transplant

Date last follow up Scr- last follow up visit GFR- last follow up visit

posttx_recurrance of LN posttx_ESRD Date of ESRD

Death Date of death

post tx_rejection Date_rejection Rejection_type

Note

Appendix 2: Ethics Approval Letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
Email: nos.ttama@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

28 January 2016

HREC REF: 033/2016

A/Prof I Okpechi
E13, Renal Unit
NGSH

Dear A/Prof Okpechi

PROJECT TITLE: OUTCOME OF RENAL TRANSPLANTATION IN PATIENTS WITH LUPUS NEPHRITIS: A SINGLE CENTRE STUDY IN CAPE TOWN- (Masters candidate Ahmed Almradi)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

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

Approval is granted for one year until the 30th January 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the Master of Medicine student Ahmed Almradi will be involved in this study.

Please quote the HREC REF in all your correspondence.

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

Yours sincerely

pp T.Burgess

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH

Appendix 3: UCT Dissertations/Doctoral & Masters Committee Approval

From: Vuyi Mgoqi <vuyi.mgoqi@uct.ac.za>
Sent: 04 ص، 10:11 2016 نوفمبر
To: ahmedalmradi25@gmail.com
Cc: Ikechi Okpechi
Subject: Almradi: Confirmation of Approval of Study Proposal

Dear Dr Almradi

Candidature Approval (ALMAHM001)

Degree	MMed in Internal Medicine
Title	Outcomes of renal transplant in patients with Lupus nephritis: a single centre study in Cape Town
Department	Medicine
Supervisor	A/Prof I Okpechi
Ethics Approval	033/2016

I am pleased to advise that the Chair of the Dissertations/Doctoral & Masters Committee has approved your candidature for the above degree on behalf of the Committee. Formal approval was obtained by publication in the Dean's Circular, PG-Med Oct2016.

Yours sincerely

Vuyi Mgoqi

Vuyiseka Mgoqi |Receptionist: PG Academic Administration |Faculty of Health Sciences | University of Cape Town | Room N2.19, Wernher & Beit North, Health Sciences Campus, Anzio Rd, Observatory, 7925 | ☎ + 27 21 406 6751 🖷 + 27 21 406 6584 | Office Hours: 08h30 - 16h30 Unavailable Hours: 13h00 - 13h30

Appendix 4: Acceptance letter for poster presentation at South African Renal Congress 2016

Dear Ahmed A Almradi

Abstract: Outcome of Renal Transplantation in Patients with Lupus Nephritis: A single centre study in Cape Town

We are pleased to inform you that your abstract has been accepted as a poster at the Congress.

Please note the following:

1. Please confirm by return email that you will present your work at the Congress.
2. If you have not yet registered, please do so as soon as possible. If you are not registered by 17 August your presentation will be removed from the programme.
3. You may be required to be at your poster during the lunch and tea breaks on Saturday.
4. Posters should be a maximum size of A0 = 841 mm in width and 1090 mm in height.
5. Materials for fixing your poster to the poster boards will be provided.
6. All accepted abstracts will be published as received as part of the Congress Proceedings in the African Journal of Nephrology. Please re-check your abstract for errors, remove any figures, tables or references, and ensure that you remain within the limit of 300 words. Your updated abstract should reach us by 17 August.
   See also http://www.sa-renalsociety.org/SARenalCongress/2016/abstracts.asp.

Best regards

The Organising Committee

www.sa-renalsociety.org/SARSCongress/2016

Appendix 5: Acceptance letter for Poster presentation at Medicine Research day UCT

DEPARTMENT OF MEDICINE

ACTIVE IN CLINICAL SERVICE, HEALTH EDUCATION AND RESEARCH

ACTING HEAD: PROFESSOR GARY MAARTENS

J floor Old Main Building Groote Schuur Hospital, Observatory, 7925, Cape Town, South Africa
Phone: +27 21 4066200 Fax: +27 21 4486815 URL: http://web.uct.ac.za/depts/medicine/

15 September 2016

Dear Dr Almradi

LETTER OF ACCEPTANCE OF SUBMITTED ABSTRACT FOR 2016 MEDICINE RESEARCH DAY

Thank you for submitting your abstract entitled **"Outcome of renal transplantation in patients with lupus nephritis: A single centre study in Cape Town"** for consideration for presentation at the 42nd Annual Department of Medicine Research Day which is to be held in Lecture Theatre II, New Groote Schuur Hospital on Thursday, 6TH October 2016. We are delighted to inform you that your abstract has been accepted for **POSTER** presentation. For the first time, Medicine Research Day will take place over a 2-day period (Wednesday 5th October and Thursday 6th October 2016). We hope you will be able to attend the exiting lectures and presentations scheduled for Thursday.

You should prepare your POSTER in a portrait format (height 109cm and width 84cm). Your poster will be presented on **Wednesday 5TH October 2016** at Klein Schuur (beside the New GSH lecture theatre 2) and you will receive notification about the time of your presentation. You should leave your poster hanging up until the end of Research Day Presentations the following day (Thursday 6th October).

If you have any questions, kindly contact Zam Ndzotyana (zam.ndzotyana@uct.ac.za).

We look forward to your participation at this year's research day program.

Yours sincerely

GARY MAARTENS

Appendix 6: SAMJ Instructions to Authors

Author Guidelines

The SAMJ has launched a new submission and tracking system. Authors will be required to register a profile on the Editorial Manager platform in order to submit a manuscript.

To submit a manuscript, please proceed to the SAMJ Editorial Manager website:

www.editorialmanager.com/samj

To access and submit an article already in production, please see the guidelines here.

Author Guidelines

Please view the Author Tutorial for guidance on how to submit on Editorial Manager.

Please take the time to familiarise yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: submissions@hmpg.co.za).

SAMJ Policies

Type of articles considered by the SAMJ

The *SAMJ* will no longer limit the articles accepted to those that have 'general medical content', but is intending to capture the spectrum of medical and health sciences, grouped by relevance to the country's burdens of disease. This content will include research in the social sciences and economics that is relevant to the medical issues around our burden of disease. Please see 'A new vision for the *SAMJ* – and a call for papers' for a full discussion of the new directions for the *SAMJ*.

We accept the following types of articles:

- Research
- Reviews

- Clinical trials
- Editorials
- In Practice (Previously Forum incl. Case Reports)
- Correspondence
- Obituaries
- Book reviews
- Ad hoc supplements e.g. guidelines, conference/congress abstracts, Festschrifts*

The following articles are by invitation only:

- Guest editorial
- Continuing Medical Education (CME)

*Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Publication Fees

All articles published in the *South African Medical Journa*l are open access and freely available online upon publication. This is made possible by applying a business model to offset the costs of peer review management, copyediting, design and production, by charging a publication fee of R5 000 (ex vat) for each research article published. The charge applies only to **Research** articles submitted after 1 March 2017. The publication fee is standard and does not vary based on length, colour, figures, or other elements.
When submitting a Research article to the *SAMJ*, the submitting author must agree to pay the publication fee should the article be accepted for publication. The publication fee is payable when your manuscript is editorially accepted and before production commences for

publication. The submitting author will be notified that payment is due and given details on the available methods of payment. Prompt payment is advised; the article will not enter into production until payment is received.
Queries can be directed to claudian@hmpg.co.za.
Please refer to the section on 'Sponsored Supplements' regarding the publication of supplements, where a charge is applicable. Queries can be directed to dianes@hmpg.co.za or claudian@hmpg.co.za

Authorship

Named authors must consent to publication. Authorship should be based on: (*i*) substantial contribution to conceptualisation, design, analysis and interpretation of data; (*ii*) drafting or critical revision of important scientific content; or (*iii*) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions.

Author contributions should be listed/described in the manuscript.

Conflicts of interest

Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude publication of an article. However, we aim to ensure that, in such cases, readers have all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc.) with relevant individuals or organisations connected to the topic of the paper, and any association with a

product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript.

If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the National Health Research Database. Research involving human subjects must be conducted according to the principles outlined in the Declaration of Helsinki. Please refer to the National Department of Health's guideline on structures to ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's Researchers have been adhered to.

Clinical trials

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. All clinical trial reports must also contain a data sharing statement as per the recommendations of the ICMJE. Statements are to indicate:

- whether individual identified participant data will be shared;

- what data in particular will be shared; whether additional, related documents will be available;
- When the data will become available and for how long; by what access criteria data will be shared.

Please see the ICJME announcement for further details and illustrative examples of data sharing statements: ICMJE Data Sharing Statements for Clinical Trials

Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The SAMJ therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrolment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Protection of rights to privacy

Patient

Information that would enable identification of individual patients should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) has given informed written consent for publication and distribution. We further recommend that the published article is disseminated not only to the involved researchers but also to the patients/participants from whom the data was drawn. Refer to Protection of Research Participants. The signed consent form should be submitted with the manuscript to enable verification by the editorial team.

Other individuals

Any individual who is identifiable in an image must provide written agreement that the image may be used in that context in the *SAMJ.*

Copyright notice

Copyright remains in the Author's name. The work is licensed under a Creative Commons Attribution - Non-commercial Works License. Authors are required to complete and sign an Author Agreement form that outlines Author and Publisher rights and terms of publication. The **Author Agreement form** should be uploaded along with other submissions files and any submission will be considered incomplete without it.

Material submitted for publication in the *SAMJ* is accepted provided it has not been published or submitted for publication elsewhere. Please inform the editorial team if the main findings of your paper have been presented at a conference and published in abstract form, to avoid copyright infringement. The *SAMJ* does not hold itself responsible for statements made by the authors.

Previously published images

If an image/figure has been previously published, permission to reproduce or alter it must be obtained by the authors from the original publisher and the figure legend must give full credit to the original source. This credit should be accompanied by a letter indicating that permission to reproduce the image has been granted to the author/s. This letter should be uploaded as a supplementary file during submission.

Privacy statement

The *SAMJ* is committed to protecting the privacy of its website and submission system users. The names, personal particulars and email addresses entered in the website or submission system will not be made available to third parties without the user's permission or due process. By registering to use the website or submission system, users consent to receive communication from the *SAMJ* or its publisher HMPG on matters relating to the journal or associated publications. Queries with regard to privacy may be directed to publishing@hmpg.co.za.

Ethnic/race classification

Use of racial or ethnicity classifications in research is fraught with problems. If you choose to use a research design that involves classification of participants based on race or ethnicity, or discuss issues with reference to such classifications, please ensure that you include a detailed rationale for doing so, ensure that the categories you describe are carefully defined, and that socioeconomic, cultural and lifestyle variables that may underlie perceived racial disparities are appropriately controlled for. Please also clearly specify whether race or ethnicity is classified as reported by the patient (self-identifying) or as perceived by the investigators. Please note that is not appropriate to use self-reported or investigator-assigned racial or ethnic categories for genetic studies.

Continuing Professional Development (CPD)

SAMJ is an HPCSA-accredited service provider of CPD materials. Principal authors can earn up to 15 CPD continuing education units (CEUs) for publishing an article; co-authors are eligible to earn up to 5 CEUs; and reviewers of articles can earn 3 CEUs. Each month, *SAMJ* also publishes a CPD-accredited questionnaire relating to the academic content of the journal. Successful completion of the questionnaire with a pass rate of 70% will earn the reader 3 CEUs. Administration of our CPD programme is managed by Medical Practice Consulting. To complete questionnaires and obtain certificates, please visit MRP Consulting

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.

- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state ‘none’.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.

- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. the respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.

- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

**NB: Copyeditors cannot be expected to pick up and correct errors writ the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'

- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counsellors. J Genet Counsel 2008; 17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

- Research
- Editorials
- CME
- In Practice and Case reports
- Reviews
- Clinical trials
- Correspondence
- Obituaries
- Book reviews
- Guidelines

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary

outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text.

Structured abstract

- This should be 250-400 words, with the following recommended headings:
    - **Background:** why the study is being done and how it relates to other published work.
    - **Objectives:** what the study intends to find out
    - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, and any specific analyses that were done on the data.
    - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
    - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- Systematic reviews.

CME (by invite only)

CME is intended to provide readers with practical, up-to-date information on medical and related matters. It is aimed at those who are not specialists in the field.

From January 2016, all CME articles will be printed in full in the *SAMJ*. Please try to adhere strictly to the guidelines on word count as we have a page limit for the print issue of the *SAMJ*. We reserve the right to place some tables and reference lists online if this is necessary for space.

In practice, this means that each CME topic usually covers two issues of the print issue of the *SAMJ*.

The guest editor, in consultation with the editor, is responsible for convening a team of authors, deciding on the subjects to be covered and for reviewing the manuscripts submitted. The

suggestion is for 4 - 5 articles, although there is some room for flexibility contingent on discussions with the editor.

For queries about these guidelines please feel free to contact the CME editor, Dr Bridget Farham, by email (ugqirha@iafrica.com) or telephone (+27 (0)21 789 2331).

Review process

The guest editor reviews the articles and returns them to the CME editor for review and final approval.

Guest editorials

Guideline word limit: 1 000 words

- Include the guest editor's personal details (qualifications, positions, affiliation, e-mail address, and a short personal profile (50words)).
- If possible, include a photograph of the author(s) at high enough resolution for print. It is preferable to provide two guest editorials, one for each issue, so that the content of the articles in each issue is covered.

Articles

Guideline word limit: 2 000 - 3 000 words

- Each article requires an abstract of ±200 words.
- The editor reserves the right to shorten articles but will send a substantially shortened article back for author approval.

Personal details

Please supply: Your qualifications, position and affiliations and MP number (used for CPD points); Address, telephone number and fax number, and your e-mail address; and a short personal profile (50words) and a few words about your current fields of interest.

In Practic

Guideline word limit: 2 000 - 3 000words

This section includes articles that would previously have been accepted into the Forum section, and case reports.

In practice articles are those that draw attention to specific issues of clinical, economic or political interest regarding medicine and healthcare in southern Africa. They are assigned to a topic:

- Case report
- Clinical practice
- Clinical alert
- Issues in medicine
- Issues in public health
- Healthcare delivery
- Consensus/Position statement
- Medicine and the environment
- Medicine and the law
- Cochrane corner

An In Practice article should follow the following format – sub-headings are not necessary, but may be used for clarity:

- Author affiliations and qualifications: to be the same as for Research. Provide all authors' names and initials, qualifications and full affiliations, and corresponding author.

- Short abstract: does not need to be structured, but should capture the essential features of the article
- Introduction: the reason for the article and the issue being addressed
- Recent research, discussion, local policy around the issue – include your own research where appropriate
- All statements should be referenced and, if opinion only, this should be stated
- Discussion: how this article adds to the discussion around a particular topic
- If a clinical practice or policy point is at issue, this needs to be emphasised, using a box with highlights if appropriate.

Essentially In practice is an opportunity for a more discursive approach to topics of clinical, economic or political importance in southern African health systems. It is not an opportunity to put forward unsubstantiated opinions!

Case reports

The *SAMJ* has recently started to accept case reports. The cases must come from Africa, preferably southern Africa unless the condition is common to all African countries, and must be either a completely new description of a clinical condition or result (use Google!) or a case that highlights important practice or management issues.

Please use the following format for case reports:

- Title of case: do not include the words 'a case report' in the title
- Summary/abstract: up to 150 words summarising the case presentation and outcome
- Background: why is this case important and why did you write it up?
- Case presentation: presenting features, medical, social, family history as appropriate
- Case management: should be according to best practice, and if not, please explain why

- Investigations, if relevant: save space by simply saying 'normal' if, for example, renal function was completely normal, rather than listing normal results, highlight the abnormal – or indeed the normal if this is clinically significant
- Differential diagnosis, if relevant
- Treatment, if relevant
- Outcome and follow-up
- Discussion – a VERY BRIEF review of similar published cases
- Teaching points: 3 - 5 bullet points
- References: as per the *SAMJ* house style
- Tables and figures: keep to a minimum. Use clinical images where relevant – we need hi-res versions for print, and identifiable persons must have a consent form
- Patient consent: please include a statement about patient consent to a written case report. This should be uploaded as a supplementary file.

Clinical trials

Guideline word limit: 4000 words

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register.
The *SAMJ* therefore requires that clinical trials be registered in the relevant public trials registry

at or before the time of first patient enrolment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Review articles

Guideline word limit: 4 000 words

These are welcome, but should be either commissioned or discussed with the Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners.

Please ensure that your article includes:

- Abstract: unstructured, of about 100-150 words, explaining the review and why it is important
- Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.
- When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
- Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

Guideline word limit: 500 words

Letters to the editor should relate either to a paper or article published by the SAMJ or to a topical issue of particular relevance to the journal's readership

- May include only one illustration or table
- Must include a correspondence address.

Book reviews

Guideline word limit: 400 words

Should be about 400 words and must be accompanied by the publication details of the book. Provide a hi-res image of the cover if possible (with permission from the copyright holder).

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Guidelines

Guidelines should always be discussed with the Editor prior to submission.

Because of the intensive review process required to ensure Guidelines are independent, evidence-based and free from commercial bias, they are usually published as a supplement to the *SAMJ*, the costs of which must be covered by sponsorship, advertising or payment by the guideline authors/association. We will provide a quote based on the expected length of the guideline and whether it is to appear online only, or in print, which must be accepted by the body putting the guidelines together before submitting the work to the SAMJ.

The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.

All guidelines should be structured according to Agree II.

Please access this website before putting the guidelines together, download the Agree 11 instrument and use this to put the guidelines together.

All submitted guidelines will be sent to the local Agree II appraisal committee for review and must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed.

A structured abstract not exceeding 400 words (recommended sub-headings: *Background, Recommendations, Conclusion*) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2.etc.) And summarised in a Table of Contents.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:

Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:

Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:

Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must* ***not*** *be used.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
    - On the Crossref homepage, paste the article title into the 'Metadata search' box.
    - Look for the correct, matching article in the list of results.
    - Click Actions > Cite
    - Alongside 'URL =' copy the URL between { }.

- Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

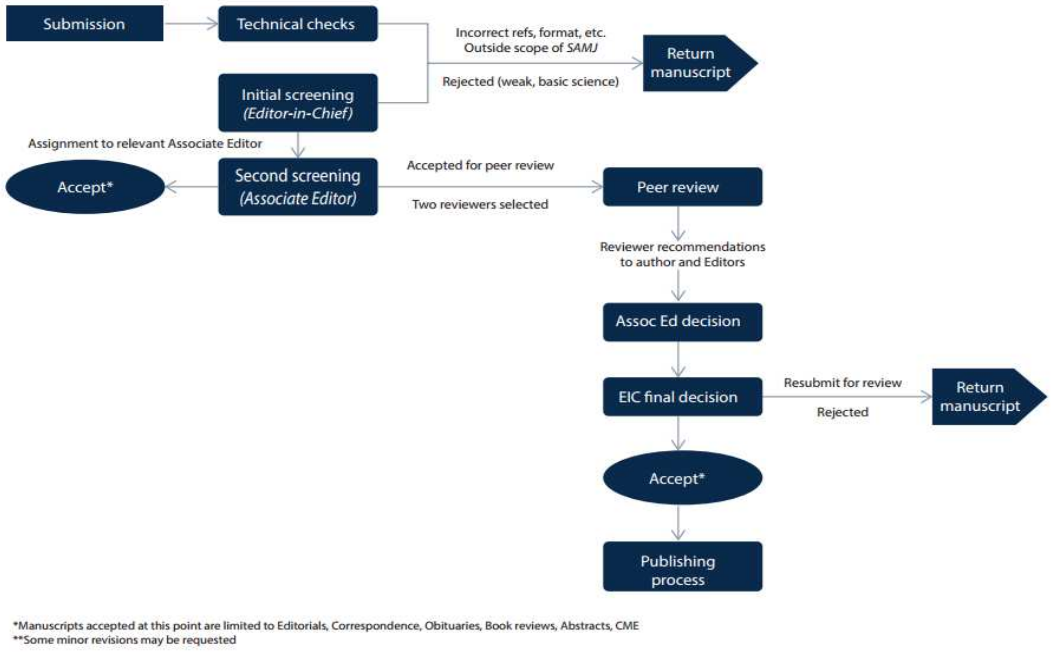
From submission to acceptance

Submission and peer-review

To submit an article:

- Please ensure that you have prepared your manuscript in line with the SAMJ requirements.
- All submissions should be submitted via Editorial Manager
- The following are required for your submission to be complete:
  - Anonymous manuscript (unless otherwise stated)
  - **Author Agreement form**
  - Manuscript
  - Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.
- Once the submission has been successfully processed on Editorial Manager, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

Peer-review process



*Manuscripts accepted at this point are limited to Editorials, Correspondence, Obituaries, Book reviews, Abstracts, CME
**Some minor revisions may be requested

Production process

The following process should usually take between 4 - 6 weeks:

1. An accepted manuscript is passed to a Managing Editor to assign to a copyeditor (CE).
2. The CE copyedits in Word, working on house style, format, spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.
3. If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.

4. The authors are typically asked to respond within 1-3 days. Any comments/changes must be clearly indicated e.g. by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.
5. The CE will finalise the article and then it will be typeset.
6. Once typeset, the CE will send a PDF of the file to the authors to complete their final check, while simultaneously sending to the 2nd-eye proof-reader.
7. The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.
8. The CE implements the authors' and proof-reader's mark-ups, finalises the file, and prepares it for the upcoming issue.

Changing contact details or authorship

Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

Publication

Online v. print

The *SAMJ* is an online journal. The online version of the journal is the one that has the widest circulation, is indexed by bibliographic databases including PubMed and SciELO, and is accessible in academic libraries. A printed edition, containing material selected by the Editor is also published each month and distributed to the membership of the South African Medical Association.

Online

- The full text of all accepted articles is published in full online, open access, within 4 - 6 weeks of acceptance.
- Citation information of each article is based on its online publication.

- You may want to make use of the advantages of online publication e.g. specify web links to other sources, images, data or even a short video.

Print

- Not all articles will be selected for print.
- An article may be selected for print in a different month from that in which it was published online.
- Research articles will appear *in abstract form only*, if selected for a print edition.

Errata and retractions

Errata

Should you become aware of an error or inaccuracy in yours or someone else's contribution after it has been published, please inform us as soon as possible via an email to publishing@hmpg.co.za,including the following details:

- Journal, volume and issue in which published
- Article title and authors
- Description of error and details of where it appears in the published article
- Full detail of proposed correction and rationale

We will investigate the issue and provide feedback. If appropriate, we will correct the web version immediately, and will publish an erratum in the next issue. The correction will be indexed, as PubMed has a function for linking errata back to the original article. All investigations will be conducted in accordance with guidelines provided by the Committee on Publication Ethics (COPE).

Retractions

Retraction of an article is the prerogative of either the original authors or the editorial team of HMPG. Should you wish to withdraw your article before publication, we need a signed statement from all the authors.

Should you wish to retract your published article, all authors have to agree in writing before publication of the retraction.

Send an email to publishing@hmpg.co.za, including the following details:

- Journal, volume and issue to which article was submitted/in which article was published
- Article title and authors
- Description of reason for withdrawal/retraction.

We will make a decision on a case-by-case basis upon review by the editorial committee in line with international best practices. Comprehensive feedback will be communicated with the authors with regard to the process. In case where there is any suspected fraud or professional misconduct, we will follow due process as recommended by the Committee on Publication Ethics (COPE), and in liaison with any relevant institutions.

When a retraction is published, it will be linked to the original article.

Indexing

The *SAMJ* has an impact factor of 1.5.

Published articles are covered by the following major indexing services. As such articles published in the *SAMJ* are immediately available to all users of these databases, guaranteed a global and African audience:

- Index Medicus (Medline/PubMed)
- ExcerptaMedica (EMBASE)
- Biological Abstracts (BIOSIS)
- Science Citation Index (SciSearch)

- Current Contents/Clinical Medicine
- Scopus
- AIM
- AJOL
- Crossref
- Sabinet
- Scielo

Sponsored supplements

Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. Named authors consent to publication and meet the requirements of authorship as set out by the journal.
2. The submission has not been previously published, nor is it before another journal for consideration.
3. The text complies with the stylistic and bibliographic requirements in **Author Guidelines**.
4. The manuscript is in Microsoft Word document format. The text is single-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.

5. Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (PDF or jpeg). These must be submitted individually as 'supplementary files' (not solely embedded in the manuscript).
6. For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.
7. Where possible, references are accompanied by a digital object identifier (DOI).
8. An abstract has been included where applicable.
9. The research was approved by a Research Ethics Committee (if applicable)
10. Any conflict of interest (or competing interests) is indicated by the author(s).

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Authors are free to copy, print and distribute their articles, in full or in part, for teaching activities, and to deposit or include their work in their own personal or institutional database or on-line website. Authors are requested to inform the Journal/Publishers of their desire/intention to include their work in a thesis or dissertation or to republish their work in any derivative form (but not for commercial use).

Material submitted for publication in the *SAMJ* is accepted provided it has not been published or submitted for publication elsewhere. Please inform the editorial team if the main findings of your paper have been presented at a conference and published in abstract form, to avoid copyright infringement.

Privacy Statement

The *SAMJ* is committed to protecting the privacy of the users of this journal website. The names, personal particulars and email addresses entered in this website will be used only for

the stated purposes of this journal and will not be made available to third parties without the user's permission or due process. Users consent to receive communication from the *SAMJ* for the stated purposes of the journal. Queries with regard to privacy may be directed to publishing@hmpg.co.za.