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FOREWORD

Mr Koh Poh Tiong
Chairman, National Kidney Foundation

When the NKF was inaugurated 47 years ago, our mission then was to render all possible services to save the lives of kidney failure patients, promote kidney transplant, encourage research on kidney diseases and carry out public education programmes on kidney diseases. I am happy to share that NKF continues to uphold this very mission today by tackling the burden of kidney failure on these fronts.

The number of kidney failure patients has been on the rise with an average of one new case every five hours. Currently, about 6,000 patients are on dialysis in Singapore. We know that diabetes and hypertension are the two contributing causes to kidney failure. We strongly encourage and support renal-related research or research on prevention. We have embarked on targeted screening programmes for high risk people such as the family members of diabetic kidney failure patients to help prevent or delay the onset of kidney failure.

I am most grateful to the Singapore Buddhist Welfare Services (SBWS) for their generous contributions towards the Venerable Yen Pei - NKF Research Fund. NKF’s 3rd Scientific Meeting is a clear indication of our commitment to care for patients with kidney disease and their family members through research. We are extremely honoured to have Assoc Professor Benjamin Ong, Director of Medical Services, Ministry of Health, as our Guest of Honor.

We look forward to greater collaboration with the restructured hospitals, other healthcare institutions, research funders and professional associations to support and advance renal research in Singapore.
MESSAGE

Mr Edmund Kwok
Chief Executive Officer, National Kidney Foundation

NKF is grateful to the Singapore Buddhist Welfare Services (SBWS) under its current leadership of Venerable Kuan Yan for its continuous support for advancing kidney-related research through the Venerable Yen Pei-NKF Research Fund. The Fund supports principal investigators and scientists from various restructured hospitals, healthcare and research institutions. Since its establishment in 2007, 91 grants have been awarded, of which 72 research projects have been completed.

NKF’s 3rd Scientific Meeting showcases the research work and findings of the projects supported by this Fund. It is a platform for researchers and healthcare professionals to share and exchange ideas as well as generate discussions to advance renal care.

The theme for this meeting, held in conjunction with the World Kidney Day, is “Advancing Care through Research”. We are privileged to have Prof Christopher Chan, Divisional Director of Nephrology and Professor of Medicine at the University Health Network, Toronto, Canada, as our distinguished guest to share with us on Nocturnal Haemodialysis and Implementation of Home Haemodialysis Programme.

I would like to take this opportunity to thank the Research Committee and Professor A Vathsala, Head & Senior Consultant, Division of Nephrology, Department of Medicine, National University Hospital and the current Chairman of the Research Committee, for ensuring good stewardship and accountability for the way the Fund is disbursed.

With the continued support of SBWS and our healthcare partners, all of us can be confident that this vital investment for the future of kidney health will continue to yield returns through the relentless work of all the researchers.
MESSAGE

Prof A Vathsala
Chairman, National Kidney Foundation, Research Committee

On behalf of the Research Committee, it gives me great pleasure to welcome you to the 3rd Scientific Meeting of the National Kidney Foundation of Singapore. The NKF of Singapore was founded in 1969 by Professor Khoo Oon Teik, a nephrologist, who inspired by personal tragedy, sought to help kidney patients in Singapore be establishing the Foundation. In the 47 years since its founding, and from this simple vision, the NKF has grown to now become the leading provider of quality dialysis care in Singapore. In addition, the NKF is the leading organization in Singapore dedicated to educating the public and screening for kidney diseases. In 2007, the NKF took the next step in furthering its vision to bring hope to kidney patients by its foray into research. The NKF became the custodian of the Venerable Yen Pei NKF Research Fund to promote research in kidney diseases in Singapore. The NKF Research Committee was established in that year, with the brief to provide stewardship and governance over these research funds. With Professor Woo Keng Thye helming the research direction since its inception, historically, these grants have funded research in a wide variety of renal related topics including Renal Physiology, Renal Cancer, Glomerulonephritis, Diabetic kidney disease, Dialysis and its complications, to name a few. To date, there have been 15 grant calls for the conduct of research under the NKF Research Fund and almost 100 grants have been awarded. Results of many of the completed projects were presented at the 1st and 2nd NKF Scientific Meetings held in 2012 and in 2014.
THE VENERABLE YEN PEI - NKF RESEARCH FUND

The Venerable Yen Pei - NKF Research Fund was set up in 2007, to make available funds specifically dedicated for renal related research.

The late Venerable Yen Pei, leader of the Singapore Buddhist Welfare Services (SBWS) shared the vision and mission of NKF in research and together with the support of the temple’s devotees, demonstrated his commitment to encourage and promote research for the advancement in renal care.

The NKF Research Committee was set up to administer the Fund to ensure good stewardship and accountability. It was helmed by Professor Woo Keng Thye, Emeritus Consultant and Advisor, Department of Renal Medicine, Singapore General Hospital, from 2007 to 2012, and subsequently by Professor A Vathsala, Head & Senior Consultant, Division of Nephrology, Department of Medicine, and National University Hospital, who is the current Chairman of the NKF Research Committee.

The projects funded were initially for basic science, translational and clinical research. In the last one year, the focus has been on prevention of kidney diseases and kidney failure. To date, 91 projects have been awarded through this Fund, of which 72 research projects have been completed. Sixty-five abstracts were featured in local conferences, 57 in overseas conferences and 41 published in various journals. Ten abstracts received international and national recognition.
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1345 - 1415  Nocturnal Haemodialysis - Clinical Benefits, Risks and Target Populations  
Prof Christopher T Chan  
Director, Division of Nephrology, University Health Network  
Professor of Medicine, University of Toronto

1415 - 1545  Oral Presentations

1545 - 1615  Tea Break

1615 - 1645  Implementation of Home Haemodialysis  
Prof Christopher T Chan

1645 - 1700  Presentation of Prizes and Tokens of Appreciation  
Prof A Vathsala

1700  End of Programme
Beyond Kidney Care, What Else?

Mr Edmund Kwok  
Chief Executive Officer, National Kidney Foundation

Singapore’s ageing population and steady increase of end-stage renal disease (ESRD) patients bring many challenges in the renal landscape. NKF takes a holistic approach to address these challenges. In partnership with various renal stakeholders, we have been putting in much effort into providing quality dialysis and boosting efforts to improve the psychological, physical and social aspects of patients’ health and well-being. This emphasis comes at the back of international research on the importance of quality of life and rehabilitation for dialysis patients. Also, to stem the increase in ESRD patients, we have stepped up our outreach and prevention programmes. In these past two years, we have launched a patient rehabilitation programme, a community programme advocating healthy living, and enhanced our holistic care initiatives, amongst others. We will share some of these initiatives, our pilot research findings, as well as our future plans and opportunities for partnerships with the wider renal community.
The National Kidney Foundation, Singapore was officially inaugurated in 1969. Its first dialysis centre was located in a geriatric nursing home which started functioning in 1982. Its first satellite dialysis centre was established in 1987. Successive years saw rapid growth of the dialysis programme.

In 2014, NKF operated 25 dialysis centres and 463 new patients joined the programme that year. At the end of the year, there were 2,738 prevalence haemodialysis patients.

Over the last 3 decades, the haemodialysis programme evolved with the introduction of new technology, volumetric controlled ultrafiltration, high flux synthetic membranes and better water treatment technology with ultrapure dialysate. During this time, we also witnessed changes in our understanding of dialysis adequacy, anaemia management, bone disease management and other aspects of dialysis provision. Along with these advances, there were also changes in case mix with a rapidly ageing dialysis population, with diabetes mellitus as the leading cause of kidney failure, multiple co-morbidities and higher physical and clinical dependency. This required a paradigm shift from focusing on guidelines-based outcomes to more individualised outcomes and wider focus on rehabilitation and psychosocial support.

This report presents the haemodialysis practice, patient growth, demographics, intermediate outcomes and survival rates in NKF’s haemodialysis programme. Data for the presentation was extracted from NKF’s clinical database for the year 2014.
Nocturnal home haemodialysis (NHD) has emerged as an alternate treatment option for patients with end-stage renal disease and has several established and potential clinical benefits. These clinical advantages need to be tempered against a growing appreciation of the risks of intensive home haemodialysis, including a potentially higher rate of vascular access interventions. Identifying who might be an eligible and optimal candidate for NHD is paramount to its expansion as an important form of renal replacement therapy. In this keynote lecture, a working definition of NHD will be provided. The various clinical benefits will be illustrated including:

1. Survival advantage
2. Cardiovascular benefits (e.g. improvements in blood pressure control, regression of left ventricular hypertrophy, augmentation of flow mediated vasodilation and correction of sleep apnea)
3. Enhanced solutes clearance
4. Kidney disease-specific quality of life
5. Fertility and Pregnancy Outcomes

The identification of potential target populations to whom this therapy will be discussed.
Implementation of Home Haemodialysis

Prof Christopher T Chan  
Director, Division of Nephrology, University Health Network  
Professor of Medicine, University of Toronto

There is renewed interest in home haemodialysis (HHD), which has been fuelled by encouraging clinical outcomes from observational and randomized controlled data in the forms of frequent HD.¹ However, given its benefits, home HD is relatively underutilized throughout the world. With all the positive data and the great strides made in the treatment modality, why wouldn't a patient select home HD as his or her preferred method of dialysis treatment? Most data reflect that among patients, physicians, and care providers, there is a considerable lack of knowledge about home HD and its proven attributes. To encourage international uptake of home HD, it is obvious that a pragmatic solution is needed.² This lecture will focus on a comprehensive, practical approach to clinicians who are interested in implementing home HD. The content of this lecture will include a “step by step” manual approach to setting up intensive haemodialysis.

Great advances have been made since the first home HD machine, which was made in only 3 months by the team of Drs. Scribner and Babb.³ As the evolution of renal replacement technology and practice pattern continues, the niche for home HD will likely become more dominant. Today, patients are more informed about their health and are taking a more active role in their treatment, and clinicians want to provide their patients with therapies that are the most effective and offer improved quality of life.

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Serum High-Sensitivity Troponin Concentrations in a Multi-Ethnic Asian Population of Stable Chronic Kidney Disease Patients
Teo Boon Wee

Identification of microRNAs Regulating Kidney Aquaporins, AQP2 and 3
Tan Jun Rong
Introduction:
Nephropathy is a complication of poorly-controlled diabetes. There are evidences suggesting that genetic predisposition is linked to poor outcomes. We aimed to study the association of gene polymorphisms from renin-angiotensin system (RAS) and cytokines with the progression of diabetic nephropathy.

Method:
Adult patients with diabetic nephropathy reviewed in Singapore General Hospital are recruited between 1 January 2002 and 31 December 2004. These patients are followed for more than 11 years till December 2015.

Patients' demographic, co-morbidity, medical therapy regime and laboratory data were obtained from electronic medical records. Genes of interest were analysed with TaqMan SNP Genotyping Assays and other molecular methods. Genetic polymorphisms were situated at 10 locations, including TNFalpha1 (rs1800629), IL6 (rs1800796), TGFbeta1 (rs1800470), PAI1 (4G/5G), ABCB1 (rs1045642), ABCB1 (rs1128503), ACE (I/D), AGT (M235T), AGT (T174M) and ATR1 (A1166C).

Outcomes studied were development of end stage renal failure (ESRF) and death. ESRF was defined as eGFR less than 15. The association of gene polymorphisms to the survival rate were statistically analysed. Linear mixed model for longitudinal was
used to examine the association, and survival analysis was performed with Gehan-Wilcoxon method.

Results:
We studied 200 patients with diabetic nephropathy: mean age 57.4 years, male 60.4%. The races include Chinese, Indian, Malay and other races. By the time we did the analysis on Dec 2015, 56 patients developed ESRF and 59 patients after initial diagnosis of diabetic nephropathy. Through statistical analysis, the polymorphisms ABCB1 (rs1045642) and AGT (M235T) are associated with poor outcomes of development of ESRF and death. The other gene polymorphisms are not significantly associated to the progression of diabetic nephropathy.

Conclusion:
The genetic polymorphisms AGT (M235T) and ABCB1 (rs1045642) are associated with early progression to ESRF in patients with diabetic nephropathy.
Cardiac Markers for Myocardial Infarction in Chronic Renal Failure Patients

PI: Assoc Prof Lim Swee Han

Co-PIs: JH Pek\(^1\), SH Lim\(^1\), TC Aw\(^2\), J Choo\(^3\), C Tan\(^4\), CP Yeo\(^4\), Z Lin\(^5\), CM Chan\(^3\)

Affiliations: 1. Department of Emergency Medicine, Singapore General Hospital, 2. Department of Laboratory Medicine, Changi General Hospital, 3. Department of Renal Medicine, Singapore General Hospital, 4. Department of Pathology, Singapore General Hospital, 5. Department of Emergency Medicine, National University Health System

Objectives:
Cardiac markers including Troponin I, Troponin T, Myeloperoxidase, Copeptin, Pro-adrenomedullin were obtained from chronic renal failure patients presenting to the Emergency Department (ED) with symptoms suggestive of angina. We aim to elucidate the use of cardiac marker in predicting mortality and myocardial infarction in this group of patients.

Method:
When Troponin T was done for chronic renal failure patients (serum creatinine of \(\geq 130 \mu\text{mol/L}\)) for evaluating of angina in the ED, patient consent would be obtained to perform Troponin I, Creatine Kinase-MB, Myeloperoxidase, Copeptin, Pro-adrenomedullin and glomerular filtration rate concurrently on the same specimen. Data including symptoms at presentation, cardiac history and cardiovascular risk factors, status of chronic renal failure including dialysis information, and previous levels of cardiac markers were collected in a standardised form. Patients were followed up for any primary end points defined as adverse cardiac event from cardiac related deaths, ventricular fibrillation and myocardial infarction, and secondary end point defined as all cause mortalities.
**Results:**
Eight hundred and nineteen patients were recruited, among them 60.2% were male. The median age was 67 (Range 28-97). Chest pain was the presenting symptom in 49.7% of the patients. 32.4% of the patients were on dialysis with the majority (85.7%) undergoing haemodialysis. The range of values for the cardiac markers were Troponin T (<0.01 to 12.76ng/mL), Creatine Kinase-MB (0.16 to 137IU/L.), Troponin I Dxl (0 to 78.3ng/mL), Troponin I Abbott (0 to 23.0ng/mL), Myeloperoxidase (87 to 9410pmol/L), Copeptin (6.9 to 1107pmol/L) and Pro-adrenomedullin (0.082 to 12.1nmol/L). Coronary artery disease related death accounted for 32.9% of 152 deaths which occurred within a year. One hundred and ninety one patients (23.3%) developed acute myocardial infarction within a year.

**Conclusion:**
By elucidating the elevation of the various cardiac markers in this study, clinicians can make an early diagnosis and institute prompt treatment of acute coronary syndrome in chronic renal failure patients, leading to improved survival.
Introduction:
This study is to assess the efficacy of drug eluting stent or stent graft placement after balloon angioplasty compared to balloon angioplasty alone for the treatment of cephalic arch stenosis in patients undergoing percutaneous transluminal angioplasty of haemodialysis access arteriovenous fistula (AVF) or graft (AVG) stenoses at 6 months.

Method:
From September 2012 to February 2014, 25 patients (15 males) with cephalic arch stenosis >50% were randomized to balloon angioplasty (PTA) (n=4); or PTA with drug-eluting stent placement (DES) (n=9); or PTA with stent graft placement (SG) (n=12). Mean age was 59.9 years (range 48-80). Follow-up angiograms were performed at 6 months to assess restenosis rates. Outcomes were circuit and lesion primary patency rates at 3 and 6 months.

Results:
Baseline characteristics were similar between groups. Before 6-month follow-up angiogram, all 4 patients in the PTA group (100%), 5 patients in the DES group (56 %) and 4 patients in the SG group (33%) underwent intervention. At 3 months, circuit primary patency rates in the PTA, DES and SG groups were 50%, 78% and 83% respectively (p=0.002) and lesion primary patency were 50%, 89% and 84% respectively (p= 0.002). At 6
months, circuit primary patency rates in the PTA, DES and SG groups were 0%, 22% and 67% respectively (p= 0.002) and lesion primary patency rates were 0%, 33% and 67% respectively (p= 0.002). Limitations at this point are small sample size, unequal distribution between groups and restenosis rates.

**Conclusion:**
Stent graft placement for cephalic arch stenosis significantly improved circuit and lesion primary patency compared to PTA alone and PTA with DES placement at 6 months. It would be interesting to see whether this significant trend is maintained with a larger group of patients.
Clinical Prevalence and Associated Factors of Erectile Dysfunction in Uremia

PI: Prof P Ganesan Adaikan¹

Co-PIs: A Vathsala², LC Lau¹, B Srilatha¹, ML Wong³, LH Koh², V Ma²

Affiliation: 1. Department of Obstetrics & Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore, 2. Division of Nephrology, Department of Medicine, National University Hospital, 3. Saw Swee Hock School of Public Health, National University of Singapore

Introduction:
Life expectancy of patients with uremia has been extended as a result of improvements in dialysis therapy. This accomplishment has led to a new appreciation of problems, previously ignored or not adequately addressed, that may affect the sexual well-being of patients with uremia. Erectile dysfunction (ED) is a well-known clinical concern with strong negative impact on the couple’s quality of life. It is also widely prevalent among uremia patients. This clinical study is aimed at assessing the prevalence of sexual dysfunction and the associated risk factors among male uremia patients.

Method:
The project utilized two validated screening tools – IIEF and PHQ9 to estimate the level of ED and depression respectively. General and specific history covered the clinical correlates predisposing to derangement. The study subjects comprised 200 men aged 21 - 65 years undergoing dialysis and clinical management at the National University Hospital, Singapore. Patients with duration < 90 days were excluded from the analysis. Hence, we ended up having 164 patients for the final analysis.
Results:
The proportion of “severe ED” is quite high (63.4%). Hence, we used severe ED status as the binary outcome of interest in our analyses. We had various factors to assess potential association with severe ED status. These include depression score, age, conditions (diseases), lifestyle, exercise frequency, and stress. No significant correlation was observed between ED score and depression score. However, we observed a significant higher odds of having severe ED as age increased. Smoking and alcohol consumption did not have significant association with severe ED status.

A significant higher odds of having severe ED was observed when the patients had diabetes. There was no significant relationship between medical conditions and ethnicity

Conclusion:
In conclusion, severe ED was observed in 63.4% of our patients analysed. Both diabetes and ageing were significantly associated with ED.
Chronic Kidney Disease Frequent Attendance from Patients’ Perspectives at the Emergency Department

PI: Assoc Prof Marcus Ong Eng Hock

Co-PIs: Yogeswary Pasupathi, Wan Paul Weng, Xin Xiaohui, Cass Chay Jwee Cheong, Chan Choon Meng, Choong Hui Lin, Mooppil Nandakumar, Rowena Yeo Siu-Lin

Affiliations: 1. Department of Emergency Medicine, Singapore General Hospital, 2. Division of Medicine, Singapore General Hospital, 3. Operations & Performance Management, Singapore General Hospital, 4. Department of Renal Medicine, Singapore General Hospital, 5. National Kidney Foundation, Singapore, 6. Health Services and Systems Research, Duke-NUS Medical School

Introduction:
The Asia-Pacific has seen a rising burden of chronic kidney disease (CKD), which is impacting hospitals and Emergency Departments (EDs). Patients with chronic kidney disease (CKD) contribute a disproportionately large percentage of visits to the emergency department (ED). Some of these visits could possibly be better attended to in settings other than the ED. The aim of this study is to characterize CKD patients who frequently visited and utilized the services of a tertiary ED in Singapore and better understand the underlying reasons behind frequent visits from the patient’s perspectives.

Methods:
Phase I was a retrospective descriptive study, with data obtained from ED records for a period of 1 year. Frequent Attenders (FA) were defined as those that made more than 4 visits during the study period. Subsequently, a qualitative phase II was conducted between Jan 2014 till Dec 2014. CKD patients were selected using quota sampling technique and asked the reasons for their ED visit. Patients selected were 21 years old and above, and had 4 or more visits in 12 months. A written informed consent was
obtained followed by, a face-to-face in-depth interview. The interviews were ceased when data saturation was reached.

**Results:**
A total of 264 patients who had an existing diagnosis of CKD were found to be frequent attenders. They accounted for 1821 visits in 2010, of which 468 visits had the attending diagnosis of Chronic Renal Failure. Of these visits, 437 (93.4%) required admission. Female patients with mean age of 65 years made up 52%. Patients with at least 4 underlying co-morbidities made up of 88%. Amongst the study population, hypertension, diabetes mellitus and ischemic heart disease were the top 3 co-morbidities. Patients diagnosed with End Stage Renal Failure (CKD stage 5) made up 87% of cases. Patients presented with complaints such as blocked arteriovenous fistulas (AVF), fluid overload and hypotension. Patients who visited ED on their own accord was 58% and 36% were referrals from dialysis centres. A total of 20 patients were identified in Phase II and 16 patients consented (50% male and mean age 63.62). Four main themes surfaced: perceived emergencies (patient believes condition is an emergency), perceived better quality of care (only the ED has comprehensive services to manage the condition of the individual), referrals from other care institutions and family (advised by primary doctor/ dialysis centres) and healthcare policies and limitations (referred due to protocol requirements in dialysis centre, GP or clinics). A total of 58% visited the ED on their own accord and 36% were referrals from dialysis centres.

**Conclusions:**
Frequent attenders with CKD who were subsequently admitted tend to have multiple co-morbidities and most common problems faced were associated with AVFs. A better understanding of the psychosocial and medical needs of CKD patients who are ED frequent attenders allows us to target interventions to address these issues and reduce ED attendances.
Singapore Vascular Access Outcomes Study: A Prospective Longitudinal Study

PI: Assoc Prof Jackie Ho Pei

Co-PIs: Peter Ashley Robless, Vathsala, Titus Lau, Julian Wong, Jimmy Teo, Rajat Tagore, Claude Renaud, Adeline Teo, Valerie Ma

Affiliations: Department of Cardiac, Thoracic & Vascular Surgery, National University Health System

Introduction:
The dialysis-dependent population in Singapore is increasing and haemodialysis remains the main modality for renal replacement therapy. Successful creation and usage of native vein arteriovenous fistula (AVF) or synthetic Arteriovenous fistula graft (AVG) offers a good haemodialysis access for patients, while minimizing the cost to the healthcare system. While international literature on haemodialysis access success rates is available, there is a lack of prospective data within the local context. This study aims to prospectively review the success rate of surgical haemodialysis access and identify the factors associated with its success.

Method:
A prospective, longitudinal observational study of the outcome of the various types of haemodialysis access created in National University Hospital between November 2012 and March 2014 was performed. All patients with access creation during the study period were invited to participate and those who provided consent were recruited to the study. All clinical outcomes were recorded prospectively up to 31 March 2015. Data collection includes demographic, medical co-morbidities, type and nature of vascular access created, peri-operative complications, and Fistula Used Successfully for Haemodialysis (FUSH) at 6 months. Univariate analysis for factors affecting FUSH was done using Chi-square test and T test.
Results:
A total of 139 patients with chronic renal disease were recruited during the study period with a mean age of 58.8 ±11.4 years (range 24-83 years) and a male to female ratio of 1.5:1. The accesses created include 23% radio-cephalic AVF, 41% brachiocephalic AVF, 16.5% brachio-basilic AVF with transposition and 19.4% AVG. 90 accesses (64.7%) successfully matured within 6 months (overall FUSH success). These included 68 AVFs (60.7%) and 22 AVGs (81.5%). Among the 68 FUSH AVFs, ten AVFs required assisted procedures for maturation. The average maturation time was 15.5 ±6.2 weeks (range 1.4-26 weeks) for FUSH AVFs and 10.3 ±6 weeks (range 1.3-24.9 weeks) for AVGs. Univariate analysis showed that primary (including pre-emptive cases) vascular access (p=0.037), level of experience (p=0.023) and individual trainee’s skill (p=0.028) were significant factors associated with overall FUSH rate. Secondary fistula over the same upper limb is associated with a higher success rate. The overall FUSH rate of trainees was significantly lower than that of the specialists. However, huge variation of the FUSH rate was observed between individual operators. Ethnicity and co-morbidities have no significant association with FUSH. The female gender is associated with lower AVF success rate (p=0.002), but this was not observed in the case of AVGs.

Conclusion:
Although the FUSH rate is compatible with international standards, time for maturation of AVFs is relatively longer, and huge variations in FUSH rates amongst individual operators were observed. Therefore we conclude that more structured training and continuous outcomes audit for haemodialysis access are required in Singapore.
Tenofovir Renal Toxicity in HIV-Infected Patients

PI: Dr Lawrence Lee Soon-U

Co-PIs: Nicholas S Chew, Boon Wee Teo

Affiliation: National University of Singapore, National University Health System

Introduction:
Tenofovir disoproxil fumarate (TDF) is a nucleotide analogue widely recommended in international HIV treatment guidelines. The association of TDF and renal dysfunction has remained an area of interest.

Method:
We conducted a retrospective review of all patients on TDF for 2.5 years in Tan Tock Seng Hospital and evaluated their renal function. Change of creatinine clearance (CLCr) using Cockcroft-Gault equation from baseline was calculated at 6, 12, 18 and 24 months. Mixed-effects models were used to analyze predictors of change in log transformed CLCr.

Results/Expected results:
Overall, 226 patients were included in the study. Ninety percent were male. The median age was 46 yrs old (23-82), median weight was 60 kg (IQR 53.75-68), median CD4 count was 127 cells/mm3 (IQR 38-258) and median CLCr 82.7 mL/min (IQR 71.4-101.7) on initiation of TDF. After excluding patients without baseline CLCr, 165 patients were left in the mixed effects analyses.

At baseline, the adjusted CLCr was 80.7 ml/min; this was 0.3% lower with every 1 year higher age and 0.1% higher with every 1 kg higher weight. After adjustment, there was a 3.0% (95% CI -0.8% to 6.6%) CLCr decline per year on average. This decline was 0.86% (95% CI 0.40% to 1.32%) steeper with 1 year age increase, 0.3% (95% CI 0.09 to 0.51%) steeper with 1 unit increase in baseline CLCr and 0.62% (95% CI 0.26 to 0.99%)
gentler with 1 kg increase in weight. There was no association with CD4 count, age, protease inhibitor use or existing co-morbidities.

**Conclusion:**
Treatment with TDF was associated with a gentle decline in renal function over 24 months. The decline was greater in older patients, patients with higher baseline CLCr and patients with lower body weight. The results underscore the need for monitoring of CLCr patients receiving TDF.
Serum High-Sensitivity Troponin Concentrations in a Multi-Ethnic Asian Population of Stable Chronic Kidney Disease Patients

PI: Dr Teo Boon Wee

Co-PIs: Titus Lau, Qi Chun Toh, Horng Ruey Chua, Weng Kin Wong, Sabrina Haroon, Srinivas Subramanian, Sharon Saw and Sunil Sethi on behalf of the NUHS Nephrology Clinical Research Group

Affiliations: National University of Singapore, National University Health System Nephrology Clinical Research Group

Introduction:
Serum troponins may be elevated because of reduced glomerular filtration rate (GFR), reduced renal catabolism, and subclinical myocardial injury related to volume overload in chronic kidney disease (CKD) patients. We aimed to determine the statistical normal of troponin-I (hsTnI) levels, in asymptomatic multi-ethnic Asian CKD patients using a high-sensitivity assay.

Method:
We performed a prospective observational cohort study in stable CKD patients, and examined the distribution of hsTnI levels (Abbott Diagnostics) across different strata of estimated GFR categories (<30, 30 to 60, >60 mL/min/1.73m2). Patients with end-stage renal disease on renal replacement therapy were excluded.

Results:
We studied 465 patients with mean age 60±14 years, 53% males, 36% with diabetes mellitus, and 17% with coronary artery disease. Median serum creatinine concentration was 137 µmol/L (89–208), with estimated GFR of 42 (25–73) mL/min/1.73m2. Respective patient numbers in each GFR category of >60, 30–60, and <30 mL/min/1.73m2, were 161, 154, and 150. Corresponding median hsTnI levels were 3.5, 5.9, and 8.7 ng/L; with 90th percentiles of 7.2, 16.2, 29.2 ng/L; and 99.5% percentiles of 25.7, 140.4, 176.1 ng/L, respectively. Serum hsTnI was significantly higher in men than women, or with presence of diabetes mellitus and/or cardiovascular diseases (p <0.01).
**Conclusion:**
Serum hsTnI levels and interpretation are heavily confounded by reduced GFR in stable CKD patients. Reviewing the data distribution, with aim to achieve clinical decision equipoise, we suggest taking the 90th percentile threshold for further evaluation of CKD patients presenting with acute coronary syndromes.
Identification of microRNAs Regulating Kidney Aquaporins, AQP2 and 3

PI: Prof Kandiah Jeyaseelan

Co-PIs: Tan Jun Rong, Armugam Arunmozhiarasi

Affiliation: National University of Singapore

Aims/ Objectives:
Aquaporins (AQPs) are a family of small hydrophobic, integral membrane proteins that are expressed in all living organisms. The kidney expresses eight isoforms of AQPs (AQPs 1, 2, 3, 4, 6, 7, 8 and 11) implicating their functional importance in kidney physiology. Dysregulation of these AQP molecules have been associated with various renal diseases. AQP2 is abundant in the renal collecting duct principal cells and regulates the water permeability of the renal collecting duct in response to vasopressin.

Another member of AQP family, AQP3 is also present in the collecting ducts and likely to facilitate basolateral exit of water through AQP2. In this project, we proposed to identify microRNAs (miRNAs; endogenous regulators of gene expression) that regulate the expression of these kidney aquaporins. The study of miRNAs targeting AQPs has potential therapeutic implications as well as contributes to the understanding of the molecular pathology involved.

Method:
Bioinformatics prediction was performed using several available miRNA databases. The 3’ untranslated region (3’UTR) of AQP2 and 3 were amplified using sequence specific primers by polymerase chain reaction (PCR). The fragment was sub-cloned into luciferase report vector for downstream assay to verify the miRNA interaction with the respective 3’UTR. The assay is quantified by measuring the relative luminescence which corresponds to the level of luciferase activity (dependent on
Results/ Discussion:
In *silico* analysis highlighted numerous miRNAs potentially targeting AQP2 and 3. miRNAs with significant prediction score were further verified using luciferase reporter assay. The results showed miR-125b and -197 effectively target AQP2 while miR-20a targets AQP3, where the transfection of anti-miRNA resulted in an increase in relative luminescence while there was reduction in relative luminescence in pre-miRNA. Pathway analysis was performed based on the 3 miRNAs (miR-20a, -125b and -197 targeting AQP 2 and 3. Interestingly, the pathways highlighted showed an overlap with pathways implicated in diabetes.

Conclusion/ Comments:
AQP2 is a *bone fide* target of miR-125b and -197 while AQP3 is a target of miR-20a. The identification of miRNAs targeting kidney AQPs has yield new insights into the possible molecular mechanism in diabetes induced kidney complications.

This study was supported by a research grant from the National Kidney Foundation of Singapore (NKFRC/2013/01/11).
PROJECTS FUNDED BY THE VENERABLE YEN PEI-NKF RESEARCH FUND
COMPLETED RESEARCH PROJECTS

**Urinary Concentrations of Chemokines and Cytokines in Lupus Patients**
Fong Kok Yong
Division of Medicine and Department of Rheumatology and Immunology
Singapore General Hospital

**Prospective Monitoring of Volume and Nutritional Status Using Bioimpedance Spectroscopy in Incident Peritoneal Dialysis (PD) Patients and Prospective Monitoring of Fluids Status During Episodes of Volume Overload in Prevalent**
Marjorie Foo
Department of Renal Medicine
Singapore General Hospital

**Assessment of Renal Disease Activity and Response in Lupus Nephritis – Comparison of Agreement in Rating by Rheumatologists and Renal Physicians**
Faith Chia Li-Ann
Department of Rheumatology, Allergy and Immunology
Tan Tock Seng Hospital

**Usefulness of NGAL as a Biochemical Marker for Acute Kidney Injury in Patients with Sepsis and Cardiac Failure**
Wee Choon Peng Jeremy
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**Reducing Nephrotoxicity of Vancomycin: A Prospective, Randomized Study of Continuous Versus Intermittent Infusion of Vancomycin**
Jolene Oon
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Department of Rheumatology, Allergy and Immunology
Tan Tock Seng Hospital

The Predictive Value of Immune and Genetic markers in Monitoring SLE Nephritis
Lian Tsui Yee
Department of Rheumatology, Allergy and Immunology
Tan Tock Seng Hospital

Calcijek® Supplementation & Vitamin D in Mediating Susceptibility to Fungal Infection
Louis Chai
Department of Medicine
National University Health System
Urinary Concentrations of Chemokines and Cytokines in Lupus Patients

PI: Prof Fong Kok Yong

Affiliation: Division of Medicine and Department of Rheumatology and Immunology, Singapore General Hospital

Introduction:
The study measures the urinary concentrations of specific chemokines and cytokines in lupus patients with active nephritis, inactive nephritis and without nephritis.

Method:
One hundred and one lupus urine samples were assayed for urinary MCP-1, VCAM-1, CXCL16, TNFR-1, p-selectin, TWEAK, Lipocalin and Adiponectin using ELISA kits. Patients classified into “active nephritis”, “inactive nephritis” and “non-nephritis” groups. The unpaired T test was used for comparison of cross sectional data. A p value of < 0.05 is considered significant.

Results:
Table 1 shows the mean urinary concentrations of chemokines and cytokines patients.

<table>
<thead>
<tr>
<th>Nephritis</th>
<th>MCP-1 (pg/ml)</th>
<th>TW EAK (pg/ml)</th>
<th>TNF-R1 (pg/ml)</th>
<th>CXCL-16 (pg/ml)</th>
<th>VCA M-1 (pg/ml)</th>
<th>Lipocalin (pg/ml)</th>
<th>P-Selectin (pg/ml)</th>
<th>Adiponectin (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active (n=12)</td>
<td>755</td>
<td>15</td>
<td>1732</td>
<td>95</td>
<td>3192</td>
<td>5520</td>
<td>314</td>
<td>3592</td>
</tr>
<tr>
<td>Inactive (n=28)</td>
<td>172</td>
<td>11</td>
<td>913</td>
<td>52</td>
<td>2503</td>
<td>4062</td>
<td>320</td>
<td>3690</td>
</tr>
<tr>
<td>Non Nephritis (n=61)</td>
<td>77</td>
<td>15</td>
<td>676</td>
<td>47</td>
<td>1720</td>
<td>3672</td>
<td>320</td>
<td>2312</td>
</tr>
</tbody>
</table>
In the “active nephritis” group, MCP-1, TNF-R1, VCAM-1 and Lipocalcin concentrations were significantly elevated. The “inactive nephritis” group had significantly higher MCP-1, VCAM-1 and Adiponectin concentrations than the “non-nephritis” group. Urinary concentrations of TWEAK, CXCL-16 and p-selectin did not show any significant difference between the groups.

**Conclusion:**
Lupus patients with active nephritis showed a profile of elevated urinary MCP-1, TNF-R1, VCAM-1 and Lipocalcin concentrations. Clinically inactive lupus patients exhibit elevated concentrations of MCP-1 and VCAM-1, suggesting the possibility of an ongoing low grade inflammatory process in the kidneys.

**Note:** This abstract was first presented at the 11th International Congress on SLE (Vienna, Sep 2015)
Prospective Monitoring of Volume and Nutritional Status Using Bioimpedance Spectroscopy in Incident Peritoneal Dialysis (PD) Patients and Prospective Monitoring of Fluids Status During Episodes of Volume Overload in Prevalent

PI: Dr Marjorie Foo

Affiliations: Department of Renal Medicine, Singapore General Hospital

Aims/Objectives:
The prospective longitudinal study is aimed at comparing assessment of nutrition and fluid status in PD using BCM versus standard clinical assessment of BP, weight and subjective global assessment (SGA) by dietitian.

Method:
For the nutrition arm, incident patients at the end of PD training will have baseline BCM measurements taken and dietary advice rendered. BCM and dietary assessment will be done at months 0, 1.5, 3, 6, 9 and 12 for the former and similarly for the latter minus the 9th month assessment.

For the fluid overload arm, incident patients will be assessed at routine clinic review with objective BCM measurement and subjective clinical assessment. In the prevalent patients, all admission with fluid overload will be assessed similarly with objective BCM measurement and subjective clinical assessment. The result of BCM however is blinded to the clinician for the purpose of the study.

Results/ Expected results:
The project terminated without recruiting the number of patients required due to manpower issues with coordination and also patient reluctance to return for visits pertaining to dietary advice due to financial reasons.
To date a total of 50 patients have been recruited in the nutrition arm and currently on follow up as per protocol. The results have yet to be analyzed, pending completion of data collection. Some patient demise and plan to recruit a few more to complete data. Recruitment for fluid overload has been unpredictable and less optimal, 20 cases were collected with incomplete data.

**Comments:**
The results will be analyzed once data is finalized
Assessment of Renal Disease Activity and Response in Lupus Nephritis– Comparison of Agreement in Rating by Rheumatologists and Renal Physicians

PI: Dr Faith Chia Li-Ann

Affiliation: Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital

Aims/ Objectives:
Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that occurs predominantly in women in the reproductive age group and damages tissues and organs as a result of inflammation from immune complex deposition.

Lupus nephritis (LN) is common amongst our patients with SLE and is a major contributor to the increased morbidity and mortality of these patients. Assessment of activity and response of LN is currently subjective, but there have been newly formulated measures that may help to improve management in LN. This project aims to

1. Compare the correlation of SLICC clinician consensus disease activity indices with SLAM and SLEDAI using case scenarios presented to rheumatologists and renal physicians
2. Retrospectively assess past renal disease activity using the above measures in LN patients to determine effect on current disease activity and renal function.
3. Prospectively assess activity and response using these measures in LN patients when therapy is initiated or changed.

Method:
Aim 1: Selected case scenarios will be presented to rheumatologists and renal physicians to score with a rating of 0 (no activity) to 3 (severe activity). These scenarios will include clinical data, medications, renal function tests, urinalysis and kidney biopsy results (if available). 160 scenarios have been
created through retrospective review of patients case sheets and are being uploaded to a web-based survey platform at present.
Aim 2: LN patients with a 10 year follow up will have their disease activity scored yearly using SLICC renal index, SLAM renal and SLEDAI renal indices. These will be correlated with the last measured renal disease activity and function.

Aim 3: Paired case scenarios with patient’s data 6 months apart after change in therapy will be presented to rheumatologists and renal physicians to be scored and comparison of agreement between the rating and the calculated scores obtained using established indices will be carried out using the chance-adjusted measure of agreement.

**Results/Expected Results:**
We hope that the information obtained will improve the management of LN by allowing greater uniformity of assessment of activity and response of the disease. It may also allow us to better understand the effect of renal disease activity on the renal outcome in LN, and evaluate the response of therapy more accurately.

**Comments:**
This study is currently in progress and no results are available at this time.
Usefulness of NGAL as a Biochemical Marker for Acute Kidney Injury in Patients with Sepsis and Cardiac Failure

PI: Dr Wee Choon Peng Jeremy

Affiliation: Department of Emergency Medicine, Singapore General Hospital

Introduction:
The goal of the study is to determine whether serum NGAL is useful in predicting acute kidney injury in renal impaired patients with sepsis or cardiac failure presenting to Emergency Department (ED). If proven to have a greater predictive value than serum creatinine, it then can be used to identify renal injury and interventions can be earlier applied to reverse or prevent acute kidney injury and in the long term even renal failure.

Method:
The inclusion criteria is
1. Age more than 21 years old
2. eGFR of 60 mL/min/1.73m\(^2\) (CKD EPI)
3. One of the following
   a. Primary diagnosis of cardiac failure OR
   b. At least 2 out of 4 of the following SIRS (Systemic Inflammatory Response Syndrome)
      i. Temperature greater than 38 degrees Celsius or less than 36 degrees Celsius
      ii. Respiratory rate greater than 20 breaths per minute or a PaCO\(_2\) of less than 32 mm Hg
      iii. Pulse rate of greater than 90 beats per minute
      iv. Total White Blood Count of greater than 12 000 cells/mm\(^3\) or less than 4 000 cells/mm\(^3\) or greater than 10% immature forms
   c. Require hospital admission.

The exclusion criteria is
1. Patients who are on renal replacement therapy e.g. haemodialysis or peritoneal dialysis
2. Females who are nursing or with a positive pregnancy test (pregnant)
3. Patients who have a known terminal illness
4. Patients who present in cardiac arrest
5. Patients who have a “Do Not Resuscitate” order
6. Patients with congenital heart disease
7. Patients with critical aortic stenosis
8. Patients who are not ambulant e.g. Wheelchair or bed bound

SGH Biochemistry Laboratory will provide research coordinator(s) with a list of patients with serum creatinine of ≥ 80 µmol/L. These patients are screened their eGFR via CKD-EPI calculated as well as other criteria for eligibility for recruitment. If a patient is eligible consent is obtained. Serum NGAL will be done on the remaining blood specimens taken for routine blood investigations.

Subsequently outpatient follow up records or notes will be traced and any renal replacement therapy at 3 months post admission will be noted. The renal replacement registry will be screened for any study patients requiring renal replacement therapy within 3 months post discharge.

**Outcome Measures**

1) Acute kidney injury (RIFLE criteria)
   a. New-onset 1.5- fold increase in serum creatinine
   b. 25% decrease in estimated GFR from baseline
   c. Decreased GFR that was sustained for at least 3 days despite volume resuscitation.
   d. Need for renal replacement therapy within 3 months

**Data Analysis:**
The serum NGAL will be compared between patients who developed AKI and those who did not using the Student t test for normally distributed variables and the Wilcoxon rank sum test for non normally distributed variables.

**Comments:**
The study is currently in the stage of data entry, results are not yet available.
Reducing Nephrotoxicity of Vancomycin: A Prospective, Randomized Study of Continuous Versus Intermittent Infusion of Vancomycin

**PI:** Dr Jolene Oon

**Affiliation:** Department of Medicine, National University Health System

**Introduction:**
The goal of the study is to reduce vancomycin-induced nephrotoxicity by comparing continuous or intermittent infusion.

**Method:**
Two hundred and twenty patients requiring a prolonged course of vancomycin will be enrolled from inpatient wards in hospitals in Singapore over a period of 2-3 years. Eligible patients are those with stable and normal baseline renal function requiring at least >10 days vancomycin for documented infections. The duration of treatment including hospital and OPAT will be determined by the clinician and this typically is 4-6 weeks or as clinically indicated. During treatment, patients will be routinely monitored (daily) at the OPAT centre. This includes clinical assessment for improvement of the presenting complaints, potential adverse events and complications of IV therapy. Routine serum creatinine, electrolytes, white blood cell count, liver function test, serum vancomycin concentrations and markers of renal toxicity (urine and serum NGAL, serum and urine cystatin C and urine albumin to creatinine ratio) will be performed weekly or more frequently if clinically indicated. Cultures will be repeated according to clinical need. The primary outcome will be nephrotoxicity, as defined by the Acute Kidney Injury Network (AKIN) criteria. The secondary outcomes will be the pharmacokinetics of vancomycin and sensitivity / specificity of biomarkers in detecting early nephrotoxicity.
**Expected Results:**
We hypothesize that administering vancomycin by continuous infusion is associated with a later onset and reduced incidence of nephrotoxicity.

**Outcome of Project:**
The study was expected to commence on 1st January 2012 and end on 31st December 2014 with a target of 220 subjects enrolled.

Unfortunately, DSRB approval was only received in April 2012. Therefore, the study actualized in September 2012. Since then, we had worked out on processing and storage issues for the research blood samples that we collected from the patients. Due to the amount of funding we had been granted (somewhat less than initially sought), we looked for another source of funding to support the expenses needed in processing and storage of the blood samples. We were also not able to engage a full time research assistant to work on the study during that time due to limited funding. During the same period, we were working out on the logistic issues as the study involved pharmacies and OPAT centres at both NUH and TTSH.

Until the end of August 2013, we screened more than 500 patients in both sites but were only able to enroll 12 patients into the study.

We reviewed the inclusion and exclusion criteria in order to facilitate enrolment without influencing our capacity to address the initial question. Each DSRB submission had been a slow and unyielding process.

The study was finally terminated in November 2014.
ISN/RPS Classification of Lupus Nephritis- Clinical and Outcome Correlations in a Singapore Cohort

PI: Dr Howe Hwee Siew

Affiliation: Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital

Aims/ Objectives:
Lupus nephritis (LN) affects an estimated 75% of systemic lupus erythematosus (SLE) patients, and impacts both renal and overall survival, with 10-15% developing end stage renal disease (ESRD). Renal biopsy is the gold standard for the assessment of LN, and histological findings direct therapy and aid prognosis. The advantages of the ISN/RPS 2003 classification of LN, which superseded the WHO classification, include reduced differences in assessment and reporting, and infrequent transformation between classes. LN is more severe in oriental populations, but reports of clinical correlation of the ISN/RPS classification with the outcome of LN have mainly been in non-oriental populations.

Method:
Patients with biopsy proven LN who satisfy ACR classification criteria for SLE will be selected from the database of our SLE prospective study cohort. Renal histopathological specimens of LN patients will be classified according to the ISN/RPS 2003 classification, including the activity and chronicity indices, will be correlated with data on clinical and laboratory parameters recorded in the study database, to identify variables that predict risk of renal and survival outcome as well as organ damage from SLE, as measured by the SLICC Damage Index (SDI).

Results/Expected Results:
Two hundred and fifteen SLE patients had biopsy proven LN, of which 207 had biopsy data available. Of the 172 patients with a single biopsy, the number who had Class 2, Class 3, Class 4, and Class 5 nephritis were 18, 23, 98 and 33 respectively. Of the 35 patients with more than one biopsy, the number with Class 4
were 6 (including 2 Class 4 and 5), Class 5 were 5 (including 1 with Class 3 and 5, and 1 with class 5 and 6).

Correlation of the biopsy data with clinical and laboratory parameters, renal and survival outcome is ongoing.

**Conclusion:**
To be determined, pending the completion of the data analysis.

**Acknowledgements:**
This study was funded by NKF Research Grant (NKFRC/2011/01/110) and BMRC grant 01/1/28/18/016. We thank the TTSH lupus study group for patient recruitment and sample contribution.
The Predictive Value of Immune and Genetic Markers in Monitoring SLE Nephritis

PI: Dr Lian Tsui Yee

Affiliation: Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital

Introduction:
Renal involvement (lupus nephritis or LN) is a major cause of morbidity and mortality, in systemic lupus erythematosus (SLE), and occurs early in 25-50% of patients, affecting up to 75% of patients over time. Single nucleotide polymorphism (SNP) variants of Integrin-α-M (ITGAM), a molecule critical for the adherence of neutrophils to stimulated endothelium and phagocytosis of complement coated particles; have been associated with susceptibility to SLE and LN. Our earlier study found that in our local SLE patients the most significant ITGAM SNP was rs4561481 in contrast to other studies where was the most commonly associated SNP was rs1143679.

Objectives:
To examine the association of ITGAM polymorphisms with LN and its correlation with the severity of LN.

Method:
293 Singapore SLE patients satisfying the 1997 ACR revised SLE criteria who were genotyped for 147 SNPs of ITGAM-ITGAX, will have the ITGAM SNPs correlated with variables prospectively recorded during their study visits including: current and previous disease manifestations, disease activity scored using SLAM-R and SLEDAI (which includes urine sediment, proteinuria, and creatinine), Damage index SLICC; and co-morbidities such as hypertension and therapy. Patients with LN will categorized by: activity of nephritis - activity of urine sediment by SLAM-R and SLEDAI, nephritic flare (active urine sediment, increase in proteinuria, stable or increased creatinine),nephrotic flare (increase in proteinuria), clinical subsets- asymptomatic microhaematuria+/- proteinuria,
nephritic syndrome, nephrotic syndrome, nephritic-nephrotic syndrome, and RPGN (rapidly progressive GN); clinical course-renal non-relapsers, recurrent relapsers (= 1 renal relapse), and refractory (recurrent relapsers despite appropriate conventional therapy).

**Results:**
13 SNPs spanning from 5' upstream of ITGAM to intron 5 of ITGAX showed significant association (p<3.4×10^{-4}), the strongest association being rs4561481 in the 5' upstream of ITGAM (OR=1.77 [1.34-2.32], p=4.2×10^{-5}). The risk allele (A) of the previously identified functional SNP of ITGAM (rs1143679, R77H) was observed at low frequency in our patients (1.4% in SLE vs. 0.2% in controls; p=0.039, OR=6.7 [0.83-53.42]), and did not remain significant after Bonferroni correction. Correlation of the ITGAM SNPs with LN and its severity is ongoing.

**Conclusion:**
All the 13 SNPs of ITGAM were associated with increased susceptibility to SLE. The most significant SNP was rs4561481, but not the previously identified functional SNP of ITGAM (rs1143679), suggesting contribution of other ITGAM variants to SLE in our cohort. Correlation of these SNPs with LN and its severity is ongoing.

**Acknowledgement:**
This study was funded by NKF Research Grant (NKFRC/2012/01/04) and BMRC grant 01/1/28/18/016. We thank the TTSH lupus study group for patient recruitment and sample contribution.
Calcijek® Supplementation & Vitamin D in Mediating Susceptibility to Fungal Infection

PI: Dr Louis Chai

Affiliation: 1. National University Health System, Singapore, 2. Institute of Molecular and Cell Biology, Singapore.

Aims/Objectives:
Vitamin D$_3$ is now widely accepted as a potent modulator of the immune function.

We aim to investigate and validate the sequelae of such immunomodulatory properties of vitamin D$_3$ in-vivo in a *Candida* mice infection model.

Method:
8 weeks old balb/c mice were infected with 2.5x10(5) live *C. albicans* via tail vein injection. Intra-peritoneal (IP) vitamin D$_3$ (Calcijex®) was initiated from day 3 post-infection at varying doses as indicated. Daily weight and survival were charted, and fungal burden in the kidneys were assessed 6 days post-infection. Neutrophil and macrophage recruitment were assessed following IP injection of killed Candida and extraction of peritoneal exudates at 4h and 72h respectively. Cytokine response was assessed using splenocytes from infected mice receiving vitamin D$_3$ treatment.

Results/Expected results:
Over a treatment range of 0.001-1µg/ml of Calcijex, mice which received 0.01 and 0.1µg/ml of Calcijex had significantly decreased kidney fungal burden as compared to untreated mice. Weight loss trends mirrored that of fungal burden in low dose Calcijex-treated mice which also showed improved survival. Mice which received 1µg/ml Calcijex showed increased fungemia and mortality. Recruitment of neutrophils and macrophages, and phagocytic function were not increased. Splenocytes treated with low dose Calcijex had elevated interferon-gamma and tumour necrosis factor-alpha response, while levels of these
proinflammatory cytokines were suppressed at higher dose 1µg/ml Calcijex.

Comments:
Low dose vitamin D$_3$ conferred resistance against candidemia associated with accentuated proinflammatory cytokine response. On the other hand, high dose vitamin D$_3$ mediating an anti-inflammatory profile was non-beneficial.
ONGOING RESEARCH PROJECTS

BASIC SCIENCE

Assessment of Autophagy in Renal Cells under Diabetic Conditions
Li Guodong
Department of Clinical Research, Singapore General Hospital

‘Two-Hit’ Hypothesis in the Pathogenesis of Minimal Change Nephrotic Syndrome: Delineating the Accessory Pathway
Yeo Wee Song
Department of Paediatrics, National University Hospital

CLINICAL RESEARCH

Pharmacogenetics Study of New-Onset Diabetes After Transplantation in Singapore Asian Renal Transplant Patients Receiving Calcineurin Inhibitor-Based Immunosuppression
Yau Wai Ping
Department of Pharmacy, National University of Singapore

Improving Medication Adherence in Post-renal Transplant Patients by Using Telemedicine
Ng Kar Hui
Department of Paediatrics, National University of Singapore

Heparin-Grafted Membrane for Continuous Renal Replacement Therapy in Critically Ill Patients with Bleeding Risk – A Randomized Cross-Over Study
Chua Horng-Ruey
Department of Medicine, National University Hospital
The Effectiveness of Self-Efficacy Psychoeducational Intervention in Enhancing Outcomes of Patients Undergoing Haemodialysis due to End Stage Renal Disease
He Hong-Gu
Alice Lee Centre for Nursing Studies, Yong Loo Lin School of Medicine, National University of Singapore

A Comprehensive Evaluation of Diabetes Susceptibility Genes and Disposition-Related Genes in Relation to the Development of New-Onset Diabetes After Transplantation in Asian Renal Transplant Recipients on Tacrolimus- or Cyclosporine-Based Immunosuppression
Yau Wai Ping
Department of Pharmacy, National University of Singapore

Exploring Biomarkers as Risk Factors for Cardiovascular Disease in Paediatric Chronic Kidney Disease
Isaac Desheng Liu
Shaw-NKF-NUH Children’s Kidney Centre, KTP-National University Children’s Medical Institute

Aetiologies and Clinical Trajectories Impacting Acute Nephropathy (ACTION study)
Chua Horng-Ruey
Department of Medicine, National University Hospital

Characterization of Autoantibodies (Autoantibodies to Phospholipase A2 receptor (Anti-PLA2R Ab) and Autoantibodies to Thrombospondin Type-1 Domain-Containing 7A (Anti-THSD7A)) in Patients with Idiopathic Membranous Nephropathy and their Correlation with Disease Activity and Clinical Outcomes
Mok Yanjia Irene
Department of Renal Medicine, Singapore General Hospital

Role of Zinc α2 Glycoprotein in the Development and Progression of Albuminuria in Type 2 Diabetes Patients
Moh Mei Chung
Clinical Research Unit, Khoo Teck Puat Hospital
Role of Angiomotin in the Pathogenesis of Membranous Nephropathy
Isaac Desheng Liu
Shaw-NKF-NUH Children’s Kidney Centre, KTP-National University Children’s Medical Institute

Adjustment and Adherence in Multimorbidity: A Mixed Methods Study of Patients with Diabetes and End Stage Renal Disease on Haemodialysis
Konstadina Griva
Department of Psychology, National University of Singapore

Biodegradeable Stents for Haemodialysis Vascular Access Intervention
Tan Chieh Suai
Department of Renal Medicine, Singapore General Hospital
Assessment of Autophagy in Renal Cells under Diabetic Conditions

PI: Dr Li Guodong  
Affiliation: Department of Clinical Research, Singapore General Hospital  
Expected completion date: June 2016

Aims/Objectives:
Nephropathy is a major diabetic complication leading to the end stage renal failure and thus patients may rely on dialysis for survival. Several metabolic disorders including hyperglycemia and dyslipidemia have been recognized as the risk factors for diabetic nephropathy. In addition, an elevation of free fatty acids (FFA) level is commonly observed in diabetic patients. This study investigated potential adverse effects of high FFA on kidney epithelial cells and explored underlying mechanisms.

Method:
RC124 cells (a human kidney epithelial cell line) were exposure to high concentrations (0.5 and 1 mM) of the saturated palmitic acid (PA) alone, or a mixture of equal amount of PA and the monounsaturated oleic acid (OA), for various periods (0.5, 1 or 2 days). Afterwards, cell viability and various signaling pathways were assessed by qRT-PCR, immuno-blotting and using assay kits performed on Muse Cell Analyzer.

Results/Expected results:
Morphological changes occurred after kidney epithelial cells were exposure to high FFA, displaying coarse surface and membrane blebbing. When OA was present, cell confluence was higher than that by high PA treatment alone. High PA treatment reduced (up to by 80%) cell viability in both dose- and time-dependent manner. On the contrary, co-treatment with equal amount of OA was able to prevent the adverse effects by PA to a large extent. The underlying mechanisms for high FFA effects on renal cell viability were studied by examining relevant signaling events.
High PA treatment activated caspase-3 and induced apoptotic cell death at 24 h. In addition, PA treatment evoked endoplasmic reticulum (ER) stress (as indicated by cleavage of ATF6 and increased phosphorylation of eIF2α) and other unfolded protein responses. High PA also caused induction of autophagy (assessed by detection of LC3-II) in renal cells. Both high PA-induced ER stress and autophagy occurred at 12 h, a time point prior to apoptosis occurrence, suggesting their possible causative relationship in the course of injuring cells. In contrast, co-treatment with OA abolished such PA-induced ER stress, autophagy and apoptosis of renal cells. The possible involvement of several stress-related cellular events in PA/OA effects on renal cells was also examined. High PA seemed not to activate protein kinase C nor increase reactive oxygen species. But production of ceramides was markedly increased by PA, an effect that was reversed by OA.

**Comments:**
High PA may exert lipotoxicity effects on kidney epithelial cells via induction of ER stress, autophagy and apoptosis perhaps via increased production of ceramides, which may contribute to the development of diabetic nephropathy. OA is capable of reversing high PA’s adverse action and has potential for development of targeting drugs.
Aims/Objectives:
Minimal change nephrotic syndrome (MCNS) is the commonest cause of childhood nephrotic syndrome. Studies attempting to elucidate the underlying pathogenesis of MCNS suggest a Th2 cytokine bias. Recent studies have, in addition, suggested a novel role for the costimulatory molecule B7-1 in podocytes as an inducible modifier of glomerular permselectivity and proteinuria. We have also shown that IL-13 overexpression in rats resulted in podocyte injury with downregulation of slit diaphragm proteins, and upregulation of glomerular B7-1, inducing MCNS. In-vitro IL-13 stimulation in cultured human podocytes resulted in upregulation of B7-1 expression. However, the degree of upregulation was not as marked as that seen in the glomeruli of the IL-13 overexpressed rats, suggesting the presence of an accessory pathway which may act independently or dependently via augmentation and perpetuation of B7-1 expression with consequent actin cytoskeleton rearrangement. We, therefore, hypothesized that the modulation of the podocyte actin cytoskeleton may possibly be a summative effect of direct IL-13 stimulation as well as signaling mediated by other immune mediators via an accessory pathway, on B7-1. The objective of this project is therefore to delineate the ‘accessory pathway’ in the pathogenesis of MCNS.

Method:
In order to identify the accessory pathway, microarray was performed on monocytes (key player in MCNS) isolated from MCNS patients in relapse and compared to remission and healthy controls. The differentially expressed “putative factor” identified was then validated both at the gene and protein levels using real-time PCR and ELISA. In vitro podocyte cell culture
system was used to validate the role of this putative factor in the accessory pathway in the pathogenesis of MCNS, by comparing the co-culturing effects of i) IL-13, ii) putative factor and iii) IL-13 + putative factor on podocyte morphology and expression of B7-1, TLR-4 and vav-1.

Results:
Monocyte transcription profile showed that IL-27, which is a known inducer of c-maf crucial in Th2 polarization, was noted to be 2.7 times upregulated in MCNS patients in relapse compared to remission. This increase in IL-27 gene expression was validated using quantitative real-time PCR. Consistent with the microarray results, plasma IL-27 levels were significantly higher in MCNS patients in relapse compared to remission. IL-13 stimulation in cultured human podocytes resulted in significant upregulation of B7-1 gene expression, leading to an increase in vav1 gene expression. This was associated with increased level of activated Rho, and subsequent actin cytoskeleton rearrangement. Podocytes stimulated with different concentrations of IL-27 (5 ng/ml, 10 ng/ml and 20 ng/ml) demonstrated a dose-dependent increase in gene expression for B7-1, Vav1 and TLR-4. Podocytes co-cultured with IL-27 demonstrated a greater than 1.5 fold under-expression of podocin, nephrin and dystroglycan which are key components of the slit diaphragm, as compared to unstimulated podocytes. Co-culturing podocytes with IL-27 and IL-13, however, did not reveal an anticipated summative increase in B7-1, VaV1 and TLR-4 gene expression.

Comments:
Our results suggest a plausible novel role of IL-27 in the pathogenesis of MCNS. Further studies are required to delineate the mechanistic action of IL-27 on podocyte cytoskeleton rearrangement.
Pharmacogenetics Study of New-Onset Diabetes after Transplantation in Singapore Asian Renal Transplant Patients Receiving Calcineurin Inhibitor-Based Immunosuppression

PI: Dr Yau Wai Ping
Affiliation: Department of Pharmacy, National University of Singapore
Expected completion date: June 2016

Aims/Objectives:
The primary objective of this study is to assess the genetically-mediated role of calcineurin inhibitors (CNIs), cyclosporine and tacrolimus, in the etiology of new-onset diabetes after transplantation (NODAT).

Method:
This is a genetic case-control association study nested in a retrospective cohort of Singapore Asian adult renal transplant patients receiving CNI-based immunosuppression after transplantation. Cases will include patients without pre-existing diabetes who developed NODAT after 1 year post-transplant while controls will include those who did not develop NODAT after a minimum follow-up of 1 year post-transplant. Blood samples will be collected from study participants for DNA extraction and genotyping analysis. We will estimate the association between the risk for NODAT in relation to three genetic variants in insulin secretion-related genes previously reported to be implicated in NODAT development in other Asian renal transplant recipients.

Results/Expected results:
This study is currently ongoing. The effort will contribute information on some potential genetic risk factors for NODAT that could explain differences in predisposition to CNI-associated NODAT among local renal transplant recipients.
Comments:
Findings from this study will provide insight into possible genetic predisposition for CNI-associated NODAT in local Asian renal transplant recipients, and may aid in the identification of potential genomic biomarkers for assessing the risk for CNI-related NODAT. These may aid clinicians in tailoring immunosuppressive regimens to prevent NODAT and improve patient and allograft outcomes in Singapore Asian renal transplant population.
Improving Medication Adherence in Post-renal Transplant Patients by Using Telemedicine

PI: Dr Ng Kar Hui
Affiliation: Department of Paediatrics, National University of Singapore
Expected completion date: June 2016

Aims/Objectives:
Non-adherence is a real threat to graft survival in renal transplant patients. Among paediatric renal transplant recipients in Singapore, poor adherence to medications leading to graft rejection is the most common cause of graft failure. We aimed to study if telemedicine can improve adherence among paediatric renal transplant patients known to have poor medication adherence.

Method:
We generated a novel interactive telemedicine platform linking a computer program and phone short message services (SMS), such that pre-programmed SMSes are sent at pre-determined times to patients to remind them to take their medications on time. Data on target drug levels and estimated glomerular filtration rate (eGFR) three months prior to the intervention and at the end of the study were collected. We also applied the Morisky 8 item Questionnaire at the start and end of the study. McNemar test was for data analysis before and after the intervention.

Results:
Twenty one post-renal transplant patients (mean age 16.11 ± 4.24 years and mean duration post-transplant 5.70 ± 4.11 years) were recruited. One was overseas at the time, and thus was excluded from the study. And data for two patients were excluded as target drug levels could not be defined. Of the remaining 18 patients, there was no significant difference in the proportions of achieved target drug levels during the intervention period compared to the preceding three months (mean difference = 0.6667, 95%CI -1.78 – 3.12, p = 0.574). There was no significant difference in eGFR before and after the
intervention (mean difference = 2.145, 95% CI -0.15 – 4.44, p = 0.94). There was also no correlation between the proportion of achieved target drug levels during the intervention and composite emotion scores obtained in the Morisky questionnaire. Of note, the age at transplantation correlated significantly with proportion of “in-range” drug levels (r = 0.57, p = 0.01), and the number of prior acute rejections showed a significant negative correlation with proportion of “in-range” drug levels (r = -0.63, p = 0.01).

**Comments:**
The telemedicine platform involving SMSes sent to patients to remind them to take medications on time did not result in significant improvement in drug adherence and renal function. It is likely because the platform was poorly received by the patients. We are currently designing a mobile phone app which may be better received by the patients.
Heparin-Grafted Membrane for Continuous Renal Replacement Therapy in Critically Ill Patients with Bleeding Risk – A Randomized Cross-Over Study

PI: Dr Chua Horng-Ruey  
Affiliation: Department of Medicine, National University Hospital  
Expected completion date: June 2016

Aims/Objectives:
To compare the performance and safety of heparin-grafted AN69 membrane (oXiris, Baxter) with conventional AN69 membrane (M150, Baxter), without additional circuit anticoagulation during continuous renal replacement therapy (CRRT) in critically ill patients with moderate bleeding risk.

Hypotheses:
1. The use of heparin-grafted membrane in an anticoagulation-free CRRT circuit will prolong circuit lifespan, compared with use of conventional membrane.

2. Systemic APTT will not be prolonged and bleeding risk will not be worsened with the use of heparin-grafted membrane.

Method:
Open-label randomized crossover study. 30 critically ill patients with moderate bleeding risk in need of CRRT will be randomized to commence CRRT with either membrane (heparin-grafted versus conventional) using an anticoagulation-free circuit. Up to 2 heparin-grafted and 2 conventional membranes will be used per patient, in a sequential crossover manner.

Outcomes:
Primary outcome will be difference in circuit lifespan with heparin-grafted versus conventional membrane for CRRT. Secondary outcomes will be the systemic APTT 2 hours after; circuit pressures during treatment; effluent:serum urea and creatinine ratios 4 hours into CRRT; vasopressor/inotropic score and urine output pre- and post- first filter, with either membranes.
Recruitment/Progress:
160 subjects were screened, of which 17 were enrolled. 15 completed the study and two were withdrawn, utilizing 15 oXiris versus 19 M150 filters. Hospital mortality was 47%, consistent with similar patient cohorts reported in the literature.

Comments:
The study recruitment will end by June 2016.
The Effectiveness of Self-Efficacy Psychoeducational Intervention in Enhancing Outcomes of Patients Undergoing Haemodialysis due to End Stage Renal Disease

PI: Assoc Prof He Hong-Gu
Affiliation: Alice Lee Centre for Nursing Studies, Yong Loo Lin School of Medicine, National University of Singapore
Expected completion date: June 2016

Aims/Objectives:
To develop a self-efficacy psychoeducational program and examine its effectiveness on outcomes (self-efficacy, psychological wellbeing, treatment adherence, and quality of life) of patients with end stage renal disease who undergo haemodialysis in Singapore.

Method:
A randomised controlled, two-group pretest and repeated posttests design is adopted. Patients with end stage renal disease undergoing haemodialysis, who are above 21 years old and attend to renal clinics in one of tertiary hospitals in Singapore, were recruited. Participants in the control group receive routine care. Participants in the intervention group receive a self-efficacy psychoeducational intervention in addition to the routine care. Instruments of Dialysis Specific Self-efficacy Scale, Kidney Disease Quality of Life- Short Form, Hospital Anxiety and Depression Scale, Renal Adherence Attitudes Questionnaire and Renal Adherence Behaviour Questionnaire are used to collect data at baseline, 1 month and 3 months’ follow ups after the intervention. Data collection is ongoing. Preliminary data will be analysed using IBM SPSS for Windows Version 22.0.

Results/Expected Results:
We report the preliminary results from the current data (Intervention group n = 27, control group n = 29) collected. There was no significant difference in participants’ demographic characteristics between groups. There were significant differences in depression (HADS-D) and quality of life (KDQoL).
between groups at baseline. Findings from this preliminary analysis of available data showed that the self-efficacy psychoeducational intervention for patients with ESRD had positive effect on **anxiety**; potential positive effects on **self-efficacy**, **depression** and **KDQoL**; no effects on renal adherence attitudes and behaviour. Non-significant findings on patients' self-efficacy, depression and KDQoL may be due to the small sample size in the current data analysis.

**Comments:**
Data collection is ongoing and the effects of the self-efficacy psychoeducational intervention on outcomes of patients with ESRD will be further examined.
A Comprehensive Evaluation of Diabetes Susceptibility Genes and Disposition-Related Genes in Relation to the Development of New-Onset Diabetes after Transplantation in Asian Renal Transplant Recipients on Tacrolimus- or Cyclosporine-Based Immunosuppression

**PI:** Dr Yau Wai Ping  
**Affiliation:** Department of Pharmacy, National University of Singapore  
**Expected completion date:** December 2016

**Aims/Objectives:**  
The primary objective of this proposal is to identify susceptibility alleles of relevance to the local renal transplant population in relation to new-onset diabetes after transplantation (NODAT) risk.

**Method:**  
This is a genetic case-control association study nested in a retrospective cohort of Singapore Asian adult renal transplant patients receiving tacrolimus- or cyclosporine-based immunosuppression who have previously provided DNA samples for pharmacogenetics study of NODAT. Cases will include patients without pre-existing diabetes who developed NODAT after 1 year post-transplant while controls will include those who did not develop NODAT after a minimum follow-up of 1 year post-transplant. The stored DNA samples will be processed for genotyping analysis. We will estimate the association between the risk for NODAT in relation to 15 genetic variants previously reported to be implicated in NODAT development, and genetic variants in diabetes susceptibility genes, in drug-metabolizing enzymes and drug transporters responsible for disposition of tacrolimus and cyclosporine.

**Results/Expected Results:**  
This study is currently ongoing. The effort will contribute information on potential genomic biomarkers for assessing the risk for developing NODAT among renal transplant recipients in Singapore.
Comments:
Findings from this effort will provide insight into any genetic predisposition for tacrolimus- or cyclosporine-associated NODAT in local Asian renal transplant recipients, and aid in the identification of potential genomic biomarkers for assessing the risk for tacrolimus- or cyclosporine-related NODAT. These would allow clinicians to identify high-risk patients to whom immunosuppressive regimens could be tailored or preemptive therapy could be provided early to prevent or ameliorate NODAT development, to prevent significant NODAT-related complications and improve long-term transplant survival in the Singapore Asian renal transplant population.
Exploring Biomarkers as Risk Factors for Cardiovascular Disease in Paediatric Chronic Kidney Disease

**PI:** Dr Isaac Desheng Liu  
**Affiliation:** Shaw-NKF-NUH Children’s Kidney Centre, KTP-National University Children’s Medical Institute  
**Expected completion date:** June 2017

**Aims/Objectives:**  
Children with chronic kidney disease (CKD) have increased risk of death from cardiovascular disease. This study explored novel biomarkers for early detection of arteriopathy among high-risk children with CKD.

**Method:**  
60 patients (Chronic Kidney Disease Stages 2-5D) and 60 controls (Chronic Kidney Disease Stage 1) were recruited. High resolution B-mode ultrasonography was performed on carotid, brachial and femoral arteries, and arteriopathy parameters measured included augmentation index, pulse wave velocity/height, and age-height standardized carotid and femoral intima-media thickness, stiffness parameter and flow-mediated dilatation. An Arteriopathy Score was computed by adding the scores of individual arteriopathy parameters (abnormal=1, normal=0). Ambulatory blood pressure (ABP) monitoring was performed, and diastolic and systolic BP scores were calculated by adding individual scores for 24h, wake, sleep BP index and load and BP dipping. Traditional biomarkers such as time-averaged haemoglobin, uric acid, calcium, phosphate and parathyroid hormone were examined. Novel biomarkers such as serum GDF-15, ST2, hsTNT, homocysteine, ADMA, hsCRP, NT-proBNP and urine NGAL were examined. An ROC model using the odds ratios as the risk-score from a multivariate logistic regression on the univariate significant clinical and biochemical parameters was developed.
Results/Expected results:
Preliminary analysis has been performed for 16 pre-dialysis CKD stages 3-4 (Group 1), and 25 CKD stage 5D patients (Group 2). All patients, mean age 16.2±6.6 years and CKD duration 4.2±3.7 years, had at least one abnormal arteriopathy parameter (median Arteriopathy Score=4). Only pulse wave velocity/height [PWV(ht)] was significantly different between Group 1 (3.3±0.7m/s) and Group 2 (4.1±0.9m/s) (p=0.006). Parameters which were associated with abnormal PWV (ht) (defined as ≥ 3.74m/s) were uric acid, diastolic BP score >5, GDF-15, hsTNT, ADMA and NTproBNP. The risk score model developed including these parameters had AUC of 0.806. Using a threshold score of 15, the sensitivity, specificity, PPV & NPV were, 76.2%, 85.0%, 84.2% and 77.3% respectively.

Conclusion:
Arteriopathy abnormalities were detected in all patients with CKD, with significant worsening of vascular reactivity as measured by PWV in advanced CKD stage 5. The composite risk score model developed is a useful predictor of severe arteriopathy in CKD.
Aetiologies and Clinical Trajectories Impacting Acute Nephropathy (ACTION study)

PI: Dr Chua Horng-Ruey
Affiliation: Department of Medicine, National University Hospital
Expected completion date: June 2016

Aims/Objectives:
To examine local acute kidney injury (AKI) epidemiology in tertiary care, especially non-critical care setting; evaluate influence of differently ascertained baseline/peak serum creatinine (sCr) measures and chronic kidney disease (CKD) on AKI staging and mortality prediction; and formulate risk scores for extended renal dysfunction and mortality.

Hypotheses
1. AKI aetiologies and prognosis are grossly different between community-acquired and hospital-associated AKIs, with and without critical illness and/or baseline CKD.
2. Use of nadir hospital sCr as baseline (versus past or admission sCr); and application of creatinine kinetics criteria for acute on CKD (AOCKD) (versus KDIGO); and volume-adjusted sCr, lead to substantive changes in AKI staging and improves mortality prediction.
3. Determination of predictors of 1-year mortality and extended renal dysfunction in survivors of AKI will help formulate an effective risk prediction model.

Method:
Prospective observational cohort study of consecutive adults who develop AKI on admission or during hospitalization identified by electronic AKI trigger, and fulfill the minimum KDIGO or creatinine kinetics criterion, over 1 year. AKI aetiologies, stages, profile, co-morbidities, critical illness, and nephrotoxins will be identified.
Target recruitment
10% of 30,000 unique patient admissions yearly may develop AKI.

Outcomes
Primary: All-cause hospital mortality.
Secondary: Non-fatal cardiac events, hospitalization and dialysis days, discharge or terminal sCr, extended renal dysfunction and mortality in subsequent year.

Analysis
1. Univariate comparisons of profile and aetiologies between community-acquired versus hospital-associated AKIs.
2. Net reclassification improvement in AKI staging and mortality prediction with volume-adjusted sCr and differently ascertained baselines, or modified criteria for AOCKD.
3. Multivariate logistic regression to identify predictors of extended outcomes, with derivation of risk prediction model and internal validation.

Progress
Study commenced on 1st November 2015. To date, 700 patients who fulfill criteria have been included. 300 patients have been discharged with hospital mortality of 8%. The electronic trigger and recruitment will end by 31st October 2016, followed by extended data collection and analysis.
Characterization of Autoantibodies (Autoantibodies to Phospholipase A2 Receptor (Anti-PLA2R Ab) and Autoantibodies to Thrombospondin Type-1 Domain-Containing 7A (Anti-THSD7A)) in Patients with Idiopathic Membranous Nephropathy and their Correlation with Disease Activity and Clinical Outcomes

PI: Dr Mok Yanjia Irene
Affiliation: Department of Renal Medicine, Singapore General Hospital
Expected completion date: June 2018

Aims/Objectives:
Idiopathic Membranous nephropathy (IMN) is the most common cause of adult nephrotic syndrome with an uncertain clinical outcome because of disease heterogeneity and a lack of reliable biomarkers. The characterization of phospholipase A2 receptor (PLA2R) as the major target antigen in IMN and the detection of circulating autoantibodies to PLA2R (Anti-PLA2R Ab) is a major advance in understanding this disease. The prevalence of Anti-PLA2R Ab positivity and the relationship between Anti-PLA2R Ab titres and clinical outcomes has not been thoroughly investigated in Asian patients. Given that approximately 70% -80% of patients with IMN are positive for anti-PLA2R Ab, it is thought that other glomerular antigens might be involved in the remaining 30% of patients. One such antigen, Thrombospondin Type-1 Domain-Containing 7A (THSD7A) has been identified in France. We aim to explore the prevalence of other auto-antigens including Anti-THSD7A Ab in the cohort of patients with IMN, especially in the group negative for Anti-PLA2R Ab.

Our aims
1. Determine the prevalence of Anti-PLA2R Ab positivity in all adult patients undergoing native kidney biopsy for suspected glomerulonephritides, especially in the cohort of Biopsy proven IMN.
2. Observe differences in baseline Anti-PLA2R Ab titre in those who spontaneously remit versus needing Immunosuppression (IS)
3. Observe changes in Anti-PLA2R Ab titres with different treatment protocols.
4. Explore if changes in Anti-PLA2R Ab titres predict or correlate to clinical outcomes over 12 months
5. Explore the correlation of Anti-PLA2R Ab positivity and the glomerular expression of PLA2R in the corresponding immune deposits in renal biopsy samples.
6. Explore the prevalence of Anti-THSD7A Ab in IMN patients, especially those negative for Anti-PLA2R Ab and correlate to clinical outcomes.

Method:
Prospective single centre study. All adult patients with suspected glomerulonephritis who fulfill standard clinical criteria for renal biopsy will be consented for participation. Baseline serological Anti-PLA2R and Anti-THSD7A Ab assay and glomerular antigen detection on histopathological sample will be done. Biopsy proven IMN will be further followed up for 12 months as per study protocol.

Results/Expected Results:
We will be looking to confirm that, consistent with other study populations, that there will be a high Anti-PLA2R Ab positivity specifically in patients with IMN in our population, cementing its role as a specific marker for IMN.

We hope to determine if Anti-PLA2R Ab titres correlate to clinical disease activity and outcomes in our population.

Patients with high circulating Anti-PLA2R Ab have been found to have absent PLA2R in glomerular deposits while some with no detectable Anti-PLA2R Ab had PLA2R in glomerular deposits. We hope to find the correlation of Anti-PLA2R Ab positivity and the glomerular expression of PLA2R in the corresponding immune deposits in renal biopsy samples in our population. This will better categorize patients into different groups with potential prognostic and therapeutic implications.
We hope to determine the prevalence of other auto-antigens (Anti- THSD7A Ab) in the cohort of patients with IMN and its correlation with disease course.

**Comments:**
Recruitment has begun October 2015 and the study is expected to be completed by June 2018.
Role of Zinc α2 Glycoprotein in the Development and Progression of Albuminuria in Type 2 Diabetes Patients

PI: Dr Moh Mei Chung
Affiliation: Clinical Research Unit, Khoo Teck Puat Hospital
Expected completion date: June 2018

Aims/Objectives:
Diabetic nephropathy (DN) is the major cause of chronic kidney disease that commonly leads to increased risk of cardiovascular morbidity and mortality in patients with type 2 diabetes (T2DM). It is typically characterized by microalbuminuria which heralds the onset of DN. Approximately 20%–40% of T2DM patients with microalbuminuria will progress to overt nephropathy and ultimately end-stage renal disease. Microalbuminuria is also recognized as an independent determinant of cardiovascular disease. Therefore, it is of clinical importance to identify factors that can predict the development of microalbuminuria in T2DM patients with normoalbuminuria. Previously, we have observed an increased protein expression of zinc α2 glycoprotein (ZAG) in impaired glomerular filtration rate (GFR < 60 ml/min/1.73m²) subjects with normoalbuminuria compared with those with macroalbuminuria. Consequently, we hypothesize that elevated ZAG may be associated with delay of albuminuria onset. In this study, we aim to evaluate the relationship of ZAG with the development of albuminuria in a prospective cohort of T2DM patients.

Method:
In this preliminary analysis, we included 50 T2DM subjects recruited from Khoo Teck Puat Hospital’s Diabetic Nephropathy Clinic. All patients had normal GFR (≥ 60 ml/min/1.73m²) and were normoalbuminuric [urinary albumin:creatinine ratio (ACR) < 30 mg/g] at initial evaluation, but a proportion of them progressed to microalbuminuria (ACR: 30–300 mg/g) while maintaining normal GFR during follow-up. The circulating concentration of ZAG was quantified by enzyme-linked immunosorbent assay in plasma samples obtained at the first patient visit. Spearman’s correlation and linear regression analyses were performed to
determine the association of ZAG with change in ACR (last visit’s ACR minus first visit’s ACR).

Results:
At baseline, the patients (mean age: 55 ± 9 years) had a median (interquartile range) level of ACR and ZAG of 7.0 (10.0) mg/g and 49.0 (69.2) µg/ml, respectively. After a mean follow-up of 5.4 ± 2.0 years, the median (interquartile range) change in ACR was 7.0 (114.8) mg/g and 44% of patients developed microalbuminuria. Univariate analysis revealed a correlation between ZAG and change in ACR (rho=-0.294, p=0.038). The association remained significant after adjustment for baseline covariates including age, gender, ethnicity, HbA1c, blood pressure, lipids, glomerular filtration rate and use of insulin and angiotensin converting enzyme inhibitor (B=-22.227, p=0.031).

Comments:
The data demonstrated that increased ZAG was inversely associated with deterioration of albuminuria in T2DM patients with normal renal function, suggesting that intervention targeting ZAG may influence the trajectory of albuminuria in T2DM. Nevertheless, the findings need to be validated in a larger cohort of patients in order to establish the applicability of ZAG in clinical practice.
Role of Angiomotin in the Pathogenesis of Membranous Nephropathy

PI: Dr Isaac Desheng Liu
Affiliation: Shaw-NKF-NUH Children’s Kidney Centre, KTP-National University Children’s Medical Institute
Expected completion date: June 2016

Aims/Objectives:

Idiopathic membranous nephropathy (IMN) is a clinically important disease. It is the commonest cause for nephrotic syndrome in adults, and half of patients may progress to end-stage renal failure. Despite its prevalence, the molecular mechanisms behind IMN are poorly understood. As a result, current treatment options are empirical and may be ineffective. IMN is a result of immune complex deposition in the glomerular basement membrane (GBM). However, only two human autoantigens have been identified - neutral-endopeptidase, and phospholipase A2 receptor - and the triggers for the formation of the immune complexes are still not completely understood.

In our preliminary study, we have identified a family with X-linked recessive membranous nephropathy. Exome sequencing has identified angiomotin (AMOT) as a novel candidate gene, with the mutation p.S50G in the p130-AMOT isoform. Our previous results showed that the serum from the patient who has the AMOT mutation and membranous nephropathy stained the tubular basement membranes (TBM) of normal human kidneys, consistent with his clinical phenotype. The overall aim of this study was to elucidate the pathogenetic mechanisms leading to disease phenotype from the AMOT mutation. Our specific aims are to study the expression of angiomotin and its isoforms in different cells and tissues, and the effects of the p.S50G angiomotin mutation in cultured cells and zebrafish models.
Method:
To further elucidate the function of AMOT and its mutation in cell cultures, we subcloned the full length of AMOT coding region into the pIRES-GFP vector and pCruz-HA vector. The corresponding mutated forms of AMOT were also created by a site-directed mutagenesis method. After transfecting the AMOT plasmids into HEK293 cells, AMOT localization was investigated.

Preliminary knockdown of amot gene in zebrafish using antisense Morpholino™ was performed to identify its possible role during embryogenesis in particular kidney development.

Results/Expected Results:
AMOT was found to be localized in nucleus and cell surface fractions of HEK293 cells. Current ongoing involves transfection of AMOT into cultured podocyte and tubular cells and to study distribution patterns and further downstream signaling pathways.

Our zebrafish experiments have demonstrated that zebrafish amot transcript variant X1 and X3 were present maternally and zygotically in the developing embryo (by RT-PCR). In contrast, zebrafish amot transcript variant X2 was not detected in the developing embryo. The results of the knockdown of amot in zebrafish has suggested that amot plays a crucial role in early embryo development and a lack/absence of amot protein affects gastrulation.
Aims/Objectives:
Patients with coexisting Diabetes Mellitus and End-Stage Renal Disease (DM-ESRD) represent the fastest growing and most frail subgroup of the ESRD population. Multimorbidity can intensify treatment demands and adversely impact behavioural and emotional outcomes. The study aimed to document prevalence and factors associated with psychological distress and adherence outcomes in DM-ESRD patients.

Method:
A mixed-methods study including interviews (N=61) and a cross-sectional questionnaire survey with DM-ESRD patients (N=221) in Singapore (59±9.8 years; 60.6% male; 54.8% Chinese). Administered the Hospital Anxiety and Depression Scale, UCLA Loneliness Scale, Beck Hopelessness Inventory and measures of Health Literacy, Illness/Treatment Perceptions, Nutritional Quality-of-Life and Adherence.

Results:
Interpersonal tension and challenges related to appetite and complexity of diet dominated narratives. Survey data indicated high rates of distress (43%; 46.4%; 45%; 37.1% for depression, anxiety, loneliness and hopelessness, respectively) and non-adherence (ranging between 19% to 62.9% across aspects of renal and diabetes regime components). Multivariate modelling indicated that Health Literacy dimensions (communication, support, obtaining/appraising information) and Nutritional QOL were associated with distress indicators (ps <.05). Negative illness perceptions, low health literacy (in terms of ability to find
and understand information) and distress indicators were associated with low adherence indicators (ps < .05).

**Conclusion:**
DM-ESRD patients find diet and health care communication/navigation challenging and experience psychological distress. Carefully tailored interventions are needed to support and empower patients to manage coexisting DM-ESRD.
Biodegradeable Stents for Haemodialysis Vascular Access Intervention

**PI:** Dr Tan Chieh Suai  
**Affiliation:** Department of Renal Medicine, Singapore General Hospital  
**Expected completion date:** July 2016

**Aims/Objectives:**  
The aim of the study is to develop biodegradable stents that will be able to provide sufficient radial strength to maintain the patency of the haemodialysis vascular access and yet does not leave a permanent structure within the area of treatment to preclude further or surgical revision.

**Method:**  
The proposed dialysis access biodegradeable stent is made from a blend of PLC and PLLA polymers. The stent will degrade from the inner layer to the outer layer at duration of 2 months to 12 month. Anti-proliferative and anti-thrombosis drugs, are encapsulated into the stent, and their releases are controlled over the desired period to prevent neointimal hyperplasia and thrombosis.

The biodegradeable stent will be tested in porcine AVF model to assess its patency.

**Results/Expected results:**  
Successful in vivo and vitro testing of this biodegradeable stent could potentially revolutionize the treatment of dysfunction dialysis access.
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