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FOREWORD

Prof John Wong  
Chief Executive, National University Health System

Singapore is a very different country from 45 years ago, when the National Kidney Foundation was founded on the vision of the late Professor Khoo Oon Teik, formerly Head of Medicine at the National University of Singapore.

While we have progressed economically to developed world status, renal disease too has progressed to become one of the most important causes of morbidity and mortality in Singapore. Diabetes and hypertension have become some of the most important causes of preventable renal disease. This pattern will only worsen given our current demographics, diet, and lifestyle.

The theme for today’s meeting, held in conjunction with the World Kidney Day this March, is “Advancing Care through Research”. This recognizes the critical need to do more to develop evidence-based, peer-reviewed solutions through research to prevent and delay the onset of renal disease in Singapore.

Research has always been one of the best ways to develop solutions for grand challenges. Research done in Singapore has the advantage of taking into account local culture and practices, and addresses the issue of practicality when it comes to implementation. Singapore’s Biomedical Sciences research strategy focuses on conditions which are important to Singapore. Research done here has to be to international standards and peer reviewed to be worthy of competitive scarce resources. Presentation and publication in the world’s leading scientific meetings and journals ensures acceptance by other thought leaders. The ultimate proof of benefit is adoption by the local medical community as standard of care, with concomitant improvement in outcomes with affordability and accessibility very much in mind.

Today, more than 7,100 researchers carry out biomedical sciences research and development across Singapore in universities, research institutes, public hospitals, and industry with generous support from the Agency for Science, Technology and Research (A*STAR), the Ministries of Health, Education, and Trade and Industry, Industry itself, Foundations, and Charities. More than S$1.51 billion is spent on biomedical research annually and another S$3.7 billion has been committed between 2011 and 2015.

We are deeply grateful to the Venerable Yen Pei-NKF Research Fund as it targets projects related to renal disease. We need as many “helping hands” as possible to prevent the various diseases that affect Singapore. Together I am confident that our children will have a better future.

I look forward to major progress in renal disease in Singapore as a result of your work.
Mr Koh Poh Tiong  
Chairman, National Kidney Foundation

NKF was founded in 1969 by the late Dr Khoo Oon Teik, a nephrologist, with a mission to save the lives of kidney failure patients. This was done through working together with the community, and in particular the healthcare sector, to improve the understanding of kidney disease, its causes, treatment and prevention through research.

The number of kidney failure patients has been on the rise with an average of 4 people diagnosed each day and there are currently more than 5,200 patients on dialysis in Singapore today. We foresee that this number will continue to rise if we do not do anything. We hope more can be done upstream to prevent the onset of kidney failure. Diabetes is the most common primary disease reported to cause ESRD as shown in the National Registry of Diseases Office report 2011. More can be done to educate people to manage it effectively so that the progression from diabetes to kidney failure can be delayed or better still prevented. We strongly encourage and support renal-related research.

I am grateful that the Singapore Buddhist Welfare Services (SBWS) has shared NKF’s mission and generously sponsored NKF to establish the Venerable Yen Pei – NKF Research Fund to support kidney-related research since 2007. With the enthusiasm from the renal community, we hope that research will help to not only improve the quality of renal care, but also raise awareness of kidney disease and prevention.

NKF’s 2nd Scientific Meeting is another milestone in NKF’s history and is a clear indication of our commitment to the care of patients with kidney disease through research. We are extremely honoured to have Professor John Wong, Chief Executive of the National University Health System, grace this meeting as our Guest-of-Honour.

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.

Mr Edmund Kwok  
Chief Executive Officer, National Kidney Foundation

Sharing NKF’s mission in the area of research, the late Venerable Yen Pei, leader of the Singapore Buddhist Welfare Services (SBWS) established the Venerable Yen Pei – NKF Research Fund to encourage and promote research in all aspects of kidney and kidney-related diseases.

The Venerable Yen Pei – NKF Research Fund has supported principal investigators and scientists from various Restructured Hospitals, healthcare institutions and research institutions. As of March 2014, 85 grants have been awarded, of which 44 research projects have been completed.

NKF is grateful to the late Venerable Yen Pei and the current leader of SBWS, Venerable Kuan Yan for their support in advancing renal care through kidney-related research.

NKF’s 2nd Scientific Meeting will showcase the research work and findings of the projects funded by the Venerable Yen Pei – NKF Research Fund. It will also be an opportunity for researchers and healthcare professionals to share and exchange ideas as well as generate discussions to advance renal care.

I would like to thank the Research Committee, helmed by Professor Woo Keng Thye, Emeritus Consultant, Department of Renal Medicine, Singapore General Hospital, from 2007 to 2012, and Professor A. Vathsala, Head & Senior Consultant, Division of Nephrology, Department of Medicine, National University Hospital, the current Chairman of the Research Committee, for ensuring good stewardship and accountability for the way the Fund is disbursed.
MESSAGE

Prof A. Vathsala
Chairman, National Kidney Foundation, Research Committee

The National Kidney Foundation (NKF) of Singapore was established in 1969 by the late Dr Khoo Oon Teik. The late Dr Khoo was himself spurred on to help patients with kidney failure following the tragic death of his brother in 1958 from kidney failure. The NKF of today is a testament to his vision to help kidney patients as it is the single, largest provider of dialysis care in Singapore. Beyond advocating for the highest quality care for patients with kidney disease, the NKF has led the fight against kidney failure by educating the public and screening for kidney diseases. The late Dr Khoo’s vision for improvement in the lives of patients with kidney disease also led to the establishment of the Khoo Oon Teik Professorship in 1999, an endowment fund at the National University of Singapore that supports a world-class expert in the conduct further research into kidney disease.

This vision for promoting research in kidney disease received a new lease of life with the establishment of the Venerable Yen Pei - NKF Research Fund in 2007. Professor Woo Keng Thye has been the chairman of the research committee which disbursed the funds since its inception. During his tenure until July 2012, there have been ten grant calls and 85 research grants were awarded. Results of some of the completed projects were presented at the 1st Scientific Meeting of the NKF held in February 2012. This 2nd NKF Scientific Meeting serves as the forum for projects funded by the Venerable Yen Pei-NKF Research Fund and completed subsequent to 2012.

Since July 2012, the legacy and vision for promoting research on kidney diseases in Singapore has been entrusted to the current NKF Research Committee. Our committee is humbled at being in the shadow of the giants who have led in this endeavour before us and are very much in awe of the tasks ahead. Singapore is facing an epidemic of kidney failure caused by diabetes and compounded by a rapidly ageing population. In the earlier days there were 200 new cases of end stage kidney failure annually. Today, there are over 1,000 new cases of end stage kidney failure in Singapore annually. Despite providing the highest quality dialysis, mortality on dialysis remains high at approximately 50% at 10 years. Much then needs to be done to prevent and treat kidney disease in Singapore.

There is thus a critical need to focus renal research on factors contributing to the epidemic of chronic kidney disease in our multi-ethnic Asian population, including its epidemiology, genetics, prevention and progression; risk factors associated with acute kidney injury, including its epidemiology and outcomes in an ageing population; risk factors for adverse outcomes with dialysis and novel measures to improve outcomes following dialysis or kidney transplantation. The NKF Research committee is committed to providing stewardship and leadership in bringing translational research in kidney diseases to the forefront in the coming years. We look forward to your continued support so that, together, we can advance the care for our patients through science and research.
THE VENERABLE YEN PEI – NKF RESEARCH FUND

The Venerable Yen Pei – NKF Research Fund was set up in 2007 to encourage and promote research in all aspects of kidney and kidney related diseases.

The late Venerable Yen Pei, leader of the Singapore Buddhist Welfare Services (SBWS) shared the vision and mission of the NKF in research, and with the support of the temple’s devotees, showed his commitment towards relieving the plight of kidney patients.

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 Research Committee.

The projects funded were for basic science and translational and clinical research. To date, 85 grants have been awarded through this Fund, of which 44 research projects have been completed.

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THE NKF LECTURE
Managing A Multimorbid Elderly Dialysis Population In The Community

Dr Mooppil Nandakumar
Director, Medical Services, NKF Singapore

The population across the world, including Singapore, is rapidly ageing and the dialysis population is ageing faster than general population. Our current approach to managing end stage renal failure patients in the community will prove inadequate to meet the future challenges especially in managing the multimorbid elderly patients.

There is an urgent need to develop new approaches and acquire new capabilities in the community-based centres to tackle these challenges. For elderly patients, major changes in health or function may be unrealistic. We need to redefine the outcome criteria for this group of patients by moving from guideline-based outcomes to more individualized outcome plans.

In addition to providing good quality dialysis with an individualized care plan we have to incorporate elements of geriatric rehabilitation and psychological services to provide a holistic care. We should aim to achieve good quality of life by focusing on restoring motor and cognitive function, fall prevention and identifying and treating depression. Close cooperation between the clinical team, patient and family members is a pre-requisite in achieving this aim. Advance care planning should be made available and for patients who opt to withdraw from dialysis, hospice and palliative care services should be easily accessible.

In a community-based dialysis programme, peritoneal dialysis (PD) and haemodialysis should be given equal importance. We have to develop effective measures to promote PD as an equivalent and in some elderly patients, the preferred option of renal replacement therapy. We need to highlight the specific advantages of PD especially cardiovascular tolerance, saving travel time and improving quality of life and patient satisfaction. An innovative funding model and home assisted care will make PD a preferred option for patients.

In haemodialysis we need to reorganize the way we provide service, moving away from “one size fit all” approach in standalone out-of-hospital dialysis centres. These centres are not designed, equipped or staffed to cater to frail elderly patients with multiple medical problems. We have to develop a tiered approach of care provision with high dependency, intermediate dependency and low dependency units to deal with different dependency status.

1) Community Dialysis Centres
   Low dependency patients could be dialyzed in community-based self-care centres with low staff to patient ratio incorporating easy-to-use new technologies.

2) Stand Alone Centres
   Current out patient centre will fall into intermediate care centres.

3) High Dependency Dialysis Centres
   These high dependency units are situated in the vicinity of a hospital where medical coverage is easily available. These centres will have high staff patient ratio, beds instead of chairs, higher monitoring facilities and equipped to cater to patients with high physical and medical dependency.

4) Home Haemodialysis
   Developing home haemodialysis make perfect sense as it is the most economically viable with positive health outcome. This will help free up dialysis centre space for patients requiring closer supervision.

Dialysis is not curative and renal transplantation is the closest thing to a cure for ESRD patients. It should be promoted as the most preferred option in all patients who are medically suitable for transplantation.
PLENARY LECTURES
Hemodialysis Self Management Intervention Randomised Trial (HED-SMART) – A Practical Low Intensity Intervention To Improve Adherence And Clinical Markers In Patients On Hemodialysis

PI: A/Prof Konstadina Griva1, 3

Co-PIs: Mooppil, N2, Pala DS2, Mc Banes, H3, Newman SP3

Affiliations: 1. Department of Psychology, National University of Singapore; 2. The National Kidney Foundation Singapore; 3. Health Services Research, City University, UK

Introduction:
Adherence to diet, fluid and medication is important to maximize good clinical outcomes in Hemodialysis yet it remains suboptimal and not well-understood. Prior interventions have shown to yield improvements in self-care knowledge, and behaviour yet are constrained by small samples, lack of control group and/or randomization, and short follow ups. This trial set out to examine the effect of the HED- SMART intervention on short and long-term treatment adherence indicators.

Method:
Eligible hemodialysis patients were randomized to either usual care/control (N=133) or HED-SMART intervention (N=102). Measures of self-report adherence, self-efficacy and self-management skills were collected at baseline (Time 1), 1 week post intervention (Time 2) and at 3 (Time 3) and 9 months post-intervention (Time 4). Biochemical markers and interdialytic weights gains were collected from 1 month prior baseline and randomisation to end of trial.

HED SMART is a group-based intervention designed for real world settings. It is light-touch intervention delivered by renal health care professionals over 3 core sessions and 1 booster. It aimed to enhance patients’ motivation and capability for self-management through problem solving and goals setting fluid control, diet and medication.

Results:
A total of N=235 out of participants were enrolled (response rate 49.6%) [58% male; 56.6% Chinese; mean age 53.4(±10.4) years; mean dialysis vintage 5.82(±4.76) years]. The sample was balanced across randomization conditions on all demographic, treatment, and clinical variables. Retention rates throughout the trial were 83% [Time 2]; 79.9% [Time 3]; 74.5% [Time 4]. Self report adherence behaviours [fluid; diet and medication] and skills/technique acquisition, health service navigation and self monitoring skills significantly improved from baseline to Time 2, Time 3 and Time 4 follow ups in HED SMART condition (p <.01) relative to usual care.

Participants in HED SMART also demonstrated consistent, modest improvements on all of the clinical outcomes across the study period, but between-conditions differences were not always statistically significant. IDWG were significantly lowered across all four assessments relative to baseline in HED SMART (p <.001) but remained undifferentiated with worsening at 3 months for usual care/control participants. Improvements in mineral markers were noted in HED SMART at Time 3 (p <.001) and Time 4 for potassium levels (p <.001). Phosphate levels improved in HED SMART only at Time 3 (p=.03) but these effects were not maintained at 9 months post intervention (Time 4). There were no adverse effects.

Conclusion:
HED SMART provides and effective and practical model for improving health outcomes in HD patients. The observed improvements in clinical and self-report adherence, if supported and maintained over time, could significantly reduce ESRD-related complications in the longer term. Given the feasibility of this kind of program, it has strong potential for providing effective support to many hemodialysis patients in the future.
**Immunobiology of Minimal Change Nephrotic Syndrome**

PI: Hui-Kim Yap  
Co-PIs: Chang-Yien Chan, Kar-Hui Ng, Wee Song Yeo  
Affiliation: Shaw-NKF-NUH Children’s Kidney Centre, Department of Paediatrics, KTP-National University Children’s Medical Institute, National University Health System

**Introduction:**  
Minimal change nephrotic syndrome (MCNS) is the commonest course of childhood nephrotic syndrome in Singapore and worldwide. Unfortunately, the pathogenesis of this disease is still unknown. Studies attempting to elucidate the underlying pathogenesis of MCNS suggested a Th2 cytokine bias.

**Method:**  
Our group has demonstrated that interleukin-13 (IL-13) gene expression was upregulated in CD4+ and CD8+ T-cells of children with MCNS in relapse. We have also shown that IL-13 over expression in the rat resulted in podocyte injury with downregulation of the slit diaphragm proteins, namely nephrin and podocin, and upregulation of glomerular B7-1, inducing a minimal change-like nephropathy. Recent studies have suggested a novel role for the costimulatory molecule B7-1 in podocytes as an inducible modifier of glomerular permselectivity and proteinuria. Our current research work on the IL-13 over expression nephrotic rats has identified the potential biological relevance of vav1 in the Rho signalling pathway in the glomeruli induced by B7-1, which have not been described previously. In our preliminary experiments, we also showed significant upregulation of glomerular TLR-4 expression which correlated strongly with B7-1 expression. However our IL-13 stimulated podocytes did not show any upregulation of TLR-4 suggesting that a second stimulus other than IL-13 was responsible for the glomerular TLR-4 upregulation in the IL-13 rat model.

**Conclusion:**  
Based on these findings, we propose that perpetuation of B7-1 expression with consequent actin cytoskeleton rearrangement occurred due to a summative effect of direct IL-13 stimulation as well as indirect signalling through TLR-4 mediated by other immune mediators. In conclusion, there is strong evidence of a link between the immune system and podocyte in MCNS. With better understanding of the pathways involved, targeted therapy to attenuate this disease may be a reality in the near future.
**S-Propargyl-Cysteine, A Novel Water-Soluble Modulator Of Endogenous Hydrogen Sulfide, Attenuates Disease Progress In Autosomal Dominant Polycystic Kidney Disease**

**PI:** A/Prof Zhu Yi Zhun

**Co-PIs:** Xueqi Wang, Liu Yang, Rudolf P. Wüthrich, Andreas L. Serra, Changlin Mei

**Affiliations:** 1. Department of Pharmacology, National University Singapore; 2. Kidney Institute, Division of Nephrology, Changzheng Hospital, Second Military Medical University, Shanghai, China; 3. Institute of Physiology, University of Zürich, Switzerland; 4. Division of Nephrology, University Hospital, Zürich, Switzerland

**Introduction:**
Autosomal dominant polycystic kidney disease (ADPKD) is the most common human single-gene hereditary kidney disease, characterized by the development and growth of innumerable cysts that originate from the tubular epithelium of nephrons. Mutations in the PKD1 and PKD2 genes codifying for polycystin-1 (PC1) and polycystin-2 (PC2) are the primary cause of ADPKD, resulting in disturbances of multiple cellular signalling pathways, among which, PC1 loss of function induces activation of ERK1/2 and mammalian target of rapamycin (mTOR) and inhibition of AMPK, leading to activation of a number of processes stimulating both cell proliferation and fluid secretion, contributing to cyst formation and enlargement. Hydrogen sulfide, a signaling gas, has been found to inhibit mTOR and activate AMPK in renal epithelial cells recently. However whether Hydrogen sulfide has therapeutic effect on ADPKD has never been tested before. Our study is to test whether S-Propargyl-Cysteine (SPRC), a novel water-soluble modulator of endogenous hydrogen sulfide could attenuate disease progress in Han:SPRD rat model of ADPKD.

**Method:**
Twenty-four male Han:SPRD heterozygous (Cy/+) rats were randomly assigned (n=6) to control group (Cy/+ CON), SPRC (5 mg/kg/day) treatment group (Cy/+ SPRC 5), SPRC (10 mg/kg/day) treatment group (Cy/+ SPRC 10), and SPRC (50 mg/kg/day) treatment group (Cy/+ SPRC 50). Twelve male Han:SPRD wild-type (+/+) rats were randomly assigned (n=6) to a control group (+/+ CON) and an SPRC (50 mg/kg/day) treatment group (+/+ SPRC 50). Treatment was started in 5-week-old Cy/+ or +/+ rats and lasted for 5 weeks. The rats in the SPRC treatment groups were gavaged with the designated doses of SPRC which was dissolved in saline. Control rats were gavaged with the same amount of saline. Blood and urine were collected at baseline (before treatment), at day 17 and at day 35 of treatment in all animals. All samples were stored at -20°C before measurement. Rats were killed after 5 weeks of treatment, and kidneys were harvested for morphological analysis.

**Results:**
Cy/+ rats treated with SPRC 50 mg/kg/day for 5 weeks showed a 18.9% decrease in blood urine nitrogen (BUN), 33.4% decrease in serum creatinine (sCr), with a 32.2% lower 2 kidneys/body weight (2K/BW) ratio and a 27.5% lower renal cyst index as compared with vehicle-treated Cy/+ rats. Ki67 staining revealed a significantly lower number of positive nuclei in dilated tubules and cysts of Cy/+ SPRC50 rats compared with control group. SPRC 5 and 10 mg/kg/day treatment did not show significant difference in all the parameters compared with control group in Cy/+ rats, and SRPC 50 mg/kg/day treatment had no effect on +/- rats as well.

**Conclusion:**
SPRC treatment delays the loss of renal function, retards cyst development, inhibits the dilated tubular epithelial cell proliferation, in Han:SPR C Cy/+ rats. SPRC might become a potential drug candidate to retard progressive renal failure in patients with ADPKD in the future. The mechanisms of the pathways which are influenced by SPRC will be further investigated.
Hydrogen Sulfide: A Novel Agent To Protect Kidney Against Hypertensive Renal Injury

PI: A/Prof Bian Jinsong

Co-PIs: Bhushan Vijay Napur

Affiliation: Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore

Introduction:
Hydrogen sulfide is a new gas mediator. It is produced endogenously from CSE and CBS enogenously. The present study was design to study whether H2S can protect kidneys against ischemic damage.

Method:
We induced renal ischemia by clipping one of the two kidneys of rats to restrict blood flow to the clipped kidney.

Results:
H2S treatment reversed renal hypertension induced elevations in blood pressure, plasma renin activity and angiotensin II, without significantly affecting activity of angiotensin-converting enzyme (ACE). To further study the inhibitory effect of H2S on renin, we isolated renin-rich juxtaglomerular cells from rat kidneys as they are primarily responsible for synthesis, storage and secretion of renin. We found that H2S inhibited renin release via suppression cAMP/AC pathway. We further investigate the underlying mechanism using an immortalized renin-containing renal tumor cell line (the As4.1 cells) to examine the cAMP signaling cascade. We found that both exogenously applied and endogenously produced H2S suppresses renin degranulation via regulation of intracellular cAMP level by inhibiting AC activity and stimulating PDE activity in As4.1 cells. Our findings suggest that H2S plays a critical role in regulation of renin degranulation in As4.1 and rat renin-rich kidney cells.

Conclusion:
H2S may be used to treat renal damage and renal ischemia-induced hypertension via inhibition of renin release from juxtaglomerular cells.

Extended Renal Dysfunction And Mortality From Septic Acute Kidney Injury In Critically Ill Patients

PI: Amartya Mukhopadhyay

Co-PIs: Weng Kin WONG, Dipika Agrawal, Huiming TAY, Horng Ruey CHUA, Anantharaman Vathsala

Affiliations: 1. Division of Respiratory & Critical Care Medicine, University Medicine Cluster, National University Health System, Singapore; 2. Division of Nephrology, University Medicine Cluster, National University Health System, Singapore

Introduction:
Septic patients who develop acute kidney injury (AKI) in the intensive care unit (ICU) have increased risks of ICU and hospital mortality which are proportional to the severity of AKI. Limited studies have examined the association between AKI and long-term outcomes. We aimed to examine the impact of AKI in critically ill patients with sepsis on one-year mortality and renal function, as well as the predictors for one-year outcomes in these patients.

Methods:
We conducted a single center prospective observational study. Patients with septic AKI admitted to our Medical ICU from November 2010 to October 2012 were recruited and followed up till one year after discharge. Patients with baseline chronic kidney disease (CKD) were excluded. We defined the severity of AKI by using Acute Kidney Injury Network (AKIN) classification, and subsequent CKD by using KDOQI classification.

Results:
207 patients (mean age 64 ± SD 16 years, 61% males) were recruited for analysis. 38% and 17% of patients have underlying diabetes and ischaemic heart disease (IHD) respectively. Mean (±SD) APACHE II score was 31 ± 14. 74% and 87% of patients required vasopressors and mechanical ventilation respectively. The main sources of sepsis were from respiratory (44%) and intra-abdominal (36%). 27%, 19% and 54% of patients had AKIN class 1, 2 and 3 AKI respectively; with 38% of patients requiring renal replacement therapy (RRT). The hospital mortality rate was 36%. Of these deaths, 62% were due to infections. The mortality rate for AKI survivors up to one-year post-hospital discharge was 8%. Among AKI survivors with...
available follow-up data, 33/81 (41%) have CKD (eGFR <60 ml/min/1.73m2) at one-year post-hospital discharge. Presence of IHD (OR 3.9, 95%CI 1.5-10.2; p=0.006) and abnormal serum creatinine (defined as female >90 μmol/l and male >125 μmol/l) on hospital discharge (OR 16.9, 95%CI 8.0-35.8; p<0.001) are associated with one-year mortality among AKI survivors. Age ≥ 60 years (OR 8.8, 95%CI 2.3-33.7; p=0.002) and abnormal serum creatinine on hospital discharge (OR 76.0, 95%CI 5.9-976.1; p=0.001) are associated with CKD among AKI survivors.

Conclusions:
Septic ICU patients with AKI have high risk of extended mortality up to one year after hospital discharge. AKI survivors have extended risk of CKD at one year regardless of initial AKIN stage. These results suggest the need for prolonged follow-up of AKI survivors beyond hospital discharge to mitigate the risk of mortality and morbidity.

Prevalence Of Vitamin D Deficiency In Pre-Dialysis Chronic Kidney Disease Patients In Singapore

PI: Dr Priscilla How1,2
Co-Pi: A. Vathsala2

Affiliations: 1. Department of Pharmacy, National University of Singapore; 2. Division of Nephrology, Department of Medicine, National University Hospital

Introduction:
Vitamin D deficiency is associated with secondary hyperparathyroidism and mineral and bone disorder (MBD) in chronic kidney disease (CKD). This study aimed to determine the prevalence of vitamin D insufficiency/deficiency, and the association between vitamin D status and MBD in in predialysis stage 4 and 5 CKD patients in Singapore.

Method:
Predialysis CKD patients were included in this cross-sectional study. Patient demographics, medical/medication histories and laboratory parameters [serum 25(OH)D, creatinine, phosphate (P), calcium, albumin and intact-PTH (i-PTH)] were collected and compared among patients with various CKD stages. The association between 25(OH)D and these parameters was determined by multiple linear regression.

Results:
A total of 196 patients with mean±SD eGFR of 26.4±11.2ml/min/1.73m2 were included. Vitamin D deficiency [25(OH)D concentration <15 ng/mL] and insufficiency [25(OH)D concentration 16-30 ng/mL] was found in 29.1% and 57.7% of the patients, respectively. Mean±SD serum 25(OH)D was 20.8±9.3μg/L. Female patients had lower vitamin D concentrations than males (16.9μg/L vs. 23.9μg/L; p<0.001). Vitamin D levels were also higher in Chinese (22.3μg/L) than Malay (17.3μg/L) and Indian (13.1μg/L) patients (p<0.05). Non-adjusted analyses showed higher i-PTH concentration in vitamin D deficient patients (p<0.05).

Conclusion:
Despite being a sun-rich country all year round, majority (86.8%) of predialysis CKD patients in Singapore have suboptimal vitamin D status. Lower vitamin D concentrations were found in females and in those with darker skin tone. Vitamin D deficient patients also tended to have higher P and i-PTH levels.
Cool Vs. Warm Dialysate: Comparing The Toxin Removal Outcome

PI: Prof Gade Pandu Rangaiah

Co-PIs: Vaibhav Maheshwari, Titus Lau Wai Leong, Ling Lieng Hsi, Lakshminarayanan Samavedham, Sunil Sethi

Affiliation: 1. Department of Chemical and Biomolecular Engineering, National University of Singapore; 2. Division of Nephrology, University Medicine Cluster, National University Hospital; 3. National University Heart Centre, Singapore; 4. Department of Laboratory Medicine, National University Hospital

Aims/Objectives:
The chief aim of hemodialysis is to remove the accumulated toxins in a patient’s body. At the same time, intra-dialytic stability of the patient is very important. Cool dialysate is often recommended for improving the patient stability [1]. It decreases the blood or body core temperature. This reduced blood temperature leads to vasoconstriction and prevents the sharp drop in central blood volume, and thus prevents the intra-dialytic hypotension. However, this vasoconstriction can potentially compromise the inter-compartmental toxin transfer. It is hypothesized that cool dialysate will hamper the toxin removal and warm dialysate will improve the toxin removal. In the existing literature, there is no clinical study, which has investigated the effect of dialysate temperature on toxin removal. Only one clinical study has investigated urea removal and concluded that it is unaffected by dialysate temperature [2]. However, caution should be exercised before extrapolating this conclusion to other large sized uremic toxins, because urea is very small in size.

Method:
In the present research, we compared the effect of cool (35.5°C) and warm (37°C) dialysate on uremic toxins (both large and small sized) removal. As warm dialysate may induce patient instability, only stable subjects were recruited. A total of 15 subjects were recruited for pilot clinical study.

Results/Expected results:
Results indicate that warm dialysate significantly improves the β2-microglobulin removal.

References:
Effect Of Using An Audiovisual CPR Feedback Device On Chest Compression Rate And Depth On Manikins During Training In Dialysis Centres

PI: A/Prof Marcus Ong Eng Hock1,2

Co-PIs: Jeremy Choon Peng Wee1, Mooppil Nandakumar3, Yiong Huak Chan4, Rowena Siu-Lin Yeo5, Kaldip Kaur3, V Anantharaman1, Susan Yap1

Affiliations: 1. Department of Emergency Medicine, Singapore General Hospital; 2. Office of Clinical Sciences, Duke-NUS Graduate Medical School; 3. The National Kidney Foundation Singapore; 4. Yong Loo Lin School of Medicine, National University of Singapore

Introduction:
The aim of the study is to investigate the effect of using Automated External Defibrillator (AED) audiovisual feedback on the quality of cardio-pulmonary resuscitation (CPR) in a manikin training setting.

Method:
Five cycles of 30 chest compressions were performed on a manikin without CPR prompts. After a break of at least 5 minutes the participants performed another 5 cycles with the use of real time audiovisual feedback via the ZOLL E-Series defibrillator. Performance data was obtained and analyzed.

Results:
A total of 209 dialysis center staff participated in the study. Using a feedback system resulted in a statistically significant improvement from 39.57% to 46.94% (p=0.009) of the participants being within the target compression depth of 4-5cm and a reduction in those below target from 16.45% to 11.05% (p=0.004). The use of feedback also produced a significant improvement in achieving the target for rate of chest compression (90-110 compressions per minute) from 41.27% to 53.49; (p<0.001). The mean depth of chest compressions was 4.85cm (SD=0.79) without audiovisual feedback and 4.91 (SD = 0.69) with feedback. For rate of chest compressions, it was 104.89 (SD = 13.74) vs 101.65 (SD = 10.21) respectively. The mean depth of chest compression was less in males than in females (4.61 vs 4.93cm, p = 0.011); and this trend was reversed with the use of feedback.

Conclusion:
In conclusion the use of feedback devices helps to improve the quality of CPR during training. However more studies involving cardiac arrest patients requiring CPR are required to determine if these devices improve survival.

Surface Modification Of Silicone With Covalently Immobilized And Crosslinked Agarose For Potential Application In The Inhibition Of Infection And Omental Wrapping

PI: Prof Neoh Koon Gee1

Co-PIs: Min Li, En-Tang Kang1, Titus Lau2 and Edmund Chiong3

Affiliation: 1. Department of Chemical and Biomolecular Engineering, National University of Singapore; 2. Department of Medicine, Division of Nephrology, National University Health System; 3. National Department of Urology, University Surgical Cluster, National University Health System

Introduction:
In peritoneal dialysis (PD), the catheter, usually made of silicone, has been considered as the “lifeline” of the patient. However, the PD catheter also serves as a nidus for bacterial infection. Furthermore, complications can result from fibrin deposition and omental wrapping of the catheter which obstructs the dialysate flow. Since the introduction of Tenckhoff catheter in mid-1960s, the development of new PD catheter designs has not shown convincing improvement in reducing infection and increasing the survival rates of PD patients. Thus, in recent years, modification of the catheter surface to improve its antifouling, antibacterial and hemocompatible properties has attracted increasing interest.

Method:
In our study, we covalently immobilized and crosslinked a micron-scale agarose layer on medical grade silicone film and catheter surfaces to improve its antibacterial and antifouling properties. Agarose (AG) is a neutral polysaccharide derived from agar, which is a FDA approved ingredient. In addition, heparin (HEP) was covalently incorporated into the crosslinked AG layer to further improve the silicone’s hemocompatibility. Protein adsorption, bacterial colonization, and cell and platelet adhesion on the AG and AG-HEP modified silicone were evaluated in vitro.

Results:
The AG coating reduced Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa biofilm formation by more than 2 orders of magnitude. In addition, cell and platelet adhesion and protein adsorption was also reduced by ≥ 90%. Without compromising the antibacterial and

Oral Presentations

Surface Modification Of Silicone With Covalently Immobilized And Crosslinked Agarose For Potential Application In The Inhibition Of Infection And Omental Wrapping

PI: Prof Neoh Koon Gee1

Co-PIs: Min Li, En-Tang Kang1, Titus Lau2 and Edmund Chiong3

Affiliation: 1. Department of Chemical and Biomolecular Engineering, National University of Singapore; 2. Department of Medicine, Division of Nephrology, National University Health System; 3. National Department of Urology, University Surgical Cluster, National University Health System

Introduction:
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Results:
The AG coating reduced Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa biofilm formation by more than 2 orders of magnitude. In addition, cell and platelet adhesion and protein adsorption was also reduced by ≥ 90%. Without compromising the antibacterial and
antifouling property, further improvement in hemocompatibility, as shown by the inhibition of platelet adhesion and activation, prolonged plasma recalcification time and lower hemolysis degree, was achieved by co-immobilization of 2.6 µg cm\(^{-2}\) of HEP in the agarose coating. The AG-HEP coatings are not cytotoxic to mammalian cells, and are stable for extended periods in lysozyme aqueous solution and under autoclaving at 121 °C for 20 min.

**Conclusion:**
The favourable antibacterial, antifouling and improved hemocompatible properties as well as non-cytotoxicity of the AG-modified silicone offer promising opportunities for combating infection and omental wrapping of PD catheters. The next step in our work is to carry out testing of catheters modified using our strategy in an animal model.


**COMPLETED PROJECTS**

**Contribution And Characterization Of Monocytes/Macrophage In Human Renal Cell Carcinoma**

**PI:** Dr Alvin Wong Seng Cheong

**Affiliation:** Department of Haematology Oncology, National University Hospital

**Introduction:**
Inflammation is a hallmark of cancer. One of the key inflammatory cells which infiltrate solid tumors and play a role in tumor-associated inflammation are the monocytes and macrophages. These cells in turn modulate adaptive immune cells like T-cells to orchestrate tumor progression. While much has been studied about these cells in mouse models of cancer, little is known about them in human cancer. The present study aims at investigating the role of monocytes/macrophages in human Renal Cell Carcinoma (RCC) progression and immunoregulation therein.

**Method:**
Peripheral blood mononuclear cells were isolated from RCC patients and blood monocytes purified thereof. The gene expression profile and functional activity of these monocytes were characterized to understand their phenotype and role in tumor growth. Further, to study the mechanistic basis of how RCC tumor cells shape the phenotype of these monocytes, we used an in vitro transwell system where normal monocytes and human RCC cell line were co-cultured and studied the signalling events in the monocytes that lead to their phenotypic changes. Finally, we also analysed the phenotype of macrophages in the tumor of patients to ascertain if this was similar to those of blood monocytes.

**Results:**
Gene expression profile of monocytes from RCC patients (RCC-Mo) showed upregulation of a number of genes related to inflammation and tumor promotion (e.g. TNF, CCL3, IL1B, IL8, COX2, VEGFA, MMPs), as compared to monocytes from healthy donors (Mo). Correlating with this upregulation of ‘pro-tumor’ genes, supernatants of RCC-Mo showed heightened angiogenesis and tumor cell invasion in ex vivo assays, in line with a tumor promoting phenotype at the functional level as well. A similar profile could also been reproduced in RCC cell co-cultured monocytes as well as in tumor infiltrating macrophages from RCC tumor patients.

Monocytes/macrophages activated with stimuli like LPS or Lipid A upregulate inflammatory cytokines that can trigger an effective Th1 response. Surprisingly, RCC-Mo challenged ex vivo with Lipid A, failed to induce inflammatory Th1 cytokine genes as compared with Mo, suggesting an impaired activation, which is a characteristic of the immunosuppressive M2-like macrophages. Investigating the mechanistic basis of this impaired activation of RCC-Mo by signalling assays indicated a defect in the activation of the transcription factor, NF-kappaB in these cells.

**Comments:**
Taken together, our results demonstrate an important contribution of monocytes /macrophages in human RCC. Characterization of these cells on one hand showed them to express pro-tumor genes that can directly contribute to tumor growth by modulating angiogenesis and tumor invasion, while on the other hand, these cells are defective to further activation by classical stimuli, indicating an immunosuppressive nature that possibly ‘disarms’ an effective anti-tumor immune response.

PI: Dr Law Weng Giap

Co-PIs: Kong Kok Ooi, Bernard Leung Pui Lam, Yu Chack Yung, Song Yeong Wook, Deng Yun, Chng Hiok-Hee, Betty P. Tsao and Howe Hwee Siew

Affiliations: 1. Tan Tock Seng Hospital, Singapore; 2. Center for Molecular and Human Genetics, The Research Institute at Nationwide Children’s Hospital and The Ohio State University, Columbus, OH; 3. Seoul National University, Seoul, South Korea; 4. David Geffen School of Medicine University of California Los Angeles, Los Angeles, CA; 5. UCLA School of Medicine, Los Angeles, CA

Introduction:
SLE is a systemic autoimmune disease where lupus nephritis (LN) is a major cause of morbidity and mortality. Integrin-a-M (ITGAM) is critical for the adherence of neutrophils to stimulated endothelium and phagocytosis of complement coated particles. Recently, a variant of exon 3 (rs1143679) of ITGAM was found to be associated with susceptibility to SLE and LN in several ethnic groups including oriental Chinese and Thai populations. Our aim was to examine the potential association of ITGAM SNPs in our local SLE patients.

Method:
Custom-designed arrays were employed to study 201 SNPs covering the approximately 140kb of the ITGAM-ITGAX region in 293 Singapore SLE patients vs. 243 Asian controls. All patients satisfied the 1997 ACR revised SLE criteria. In total 147 SNPs of ITGAM-ITGAX were included in analysis. Significance difference in allelic frequencies of each SNP was examined by gPLINK 1.062 software with Bonferroni adjustment for multiple testing corrections.

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 was detected at rs4561481 in the 5' upstream of ITGAM (OR=1.77 [1.34-2.32], p=4.2×10-5). The previously identified functional SNP of ITGAM (rs1143679, R77H) in European ancestry and African-American populations has shown a strong association for the risk allele (A). However, we observed a low frequency of the risk allele (A) in our patients (1.4% in SLE vs 0.2% in controls; p=0.039, OR=6.7 [0.83-53.42]), and its association with disease susceptibility did not remain significant after Bonferroni correction. To localize the underlying causal variant, linkage equilibrium (LD) analysis was examined among these 13 SNPs which were located in a strong LD block (r2=0.92-1.0), and the conditional association could not be applied to further distinguish the independent association in our SLE cohort.

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.
Improving End-Of-Life Care In Renal Patients With A Clinical Coordinated Pathway

**PI:** Dr Alethea Yee Chung Pheng

**Co-PIs:** Patricia SH Neo, Nuraishah B Zulkifle, Doreen Lau, Lina HL Choong, CM Chan

**Affiliations:** 1. Department of Palliative Medicine, National Cancer Centre Singapore, Singapore; 2. Department of Quality Management, Singapore General Hospital, Singapore; 3. Department of Renal Medicine, Singapore General Hospital, Singapore

**Introduction:**
The Liverpool Care Pathway (LCP) for the dying has been extensively used in the United Kingdom (UK) to enable patients to die a dignified death.1 In 2008, the UK National LCP Renal Steering Group published guidelines for drug prescribing in advanced chronic kidney disease with the aim of controlling common end-of-life symptoms, which were incorporated into the Renal-LCP.2 In recent years, the LCP was adapted for use in our hospital oncology ward with significant improvements in end-of-life care.3

**Method:**
The Renal-LCP was adapted for local use and implemented in 2 renal wards in Singapore General Hospital (SGH). A baseline review of 30 consecutive death records was performed and results compared to a post-implementation audit of 29 consecutive patients recruited between Jan 2010 and May 2012.

**Results:**
There were improved symptom control prior to death for patients on renal-LCP (1.6% uncontrolled symptoms in pathway group vs 13.3% in pre-implementation group), improved anticipatory prescription of medications (40.6% in pathway group vs 26.6%), reduction in patients on parenteral fluids at time of death (24.0% in pathway group vs 40.0%) and increased discontinuation of inappropriate monitoring (41.3% in pathway group vs 36.6%). While these were not statistically significant, there was a statistically significant improvement in discontinuation of non-essential medications (93.1% in pathway group vs 53.3%).

**Conclusion:**
Our results suggest a trend towards improvement in end-of-life care when using the renal-LCP in renal patients dying in a tertiary hospital. However, in view of the results of the UK independent review of the LCP conducted this year highlighting concerns with the use of LCP,4,5 this pathway is currently suspended and may be withdrawn pending results of an ongoing audit of LCP use in SGH.

**References:**
Segmental Renal Gene Expression And Functional Characterisation Of Renal Drug Transporters In A Rat Model Of Type II Diabetes In Progressive Nephropathy

PI: Prof Edmund Lee J.D

Co-PIs: Lie Michael George Limenta, Keith Rogers, Susan Mary Rogers, Vanessa Tay Shiyun and Yee Jie Yin

Affiliations: 1. National University of Singapore, Yong Loo Lin School of Medicine, Department of Pharmacology; 2. Institute of Molecular and Cell Biology Core Histopathology Laboratory, The Advanced Molecular Pathology Laboratory

Introduction:
Changes in gene expression levels of drug transporters on cell membranes may alter transporter activities, thus affecting the pharmacokinetics and pharmacodynamics of drugs. This is particularly so for the renal proximal tubular cells. As early as three decades ago, renal functions were observed to be better correlated with tubulointerstitial changes than with glomerular changes. Findings showed that renal proximal tubular cells are susceptible to a range of metabolic and haemodynamic factors particularly diabetes associated with hyperglycaemia. However, the changes in such cells do not downplay the condition of glomerular damages in progressive diabetes. Instead, the understanding of interplay between glomerulus and tubulointerstitium will provide better insights in diabetic nephropathy.

Method:
Thirty-four male Wistar rats were used in this study. They were randomly divided into five groups; Baseline (n=6), D1 (n=8) were rats which received a combination of high fat diet consisting of 35% lard and single dose streptozotocin at 35mg/kg for the induction of diabetic nephopathy and were sacrificed three weeks after streptozotocin administration, C1 (n=6) were age-matched controls for D1 group. D2 (n=8) were sacrificed eight weeks after streptozotocin administration and C2 (n=6) were age-matched controls for D2. Body weight, blood and urinary biochemical parameters are measured for signs of diabetic nephropathy. Laser capture microdissection was employed for the collection of renal proximal tubular cells. Commercially available qPCR arrays were used for the analysis of gene expression levels changes of twenty selected renal drug transporters.

Results:
Although no clinical diabetic nephropathy in diabetic rats was observed through histopathological analysis and biochemistry testing, transforming growth factor-beta expression level in renal proximal tubular cells was shown to be higher than controls. This may suggest that tubular injury occurrence came before glomerular damage. Hyperglycaemia was observed in just a week after streptozotocin administration in rats which received high fat diet-streptozotocin treatment when compared to their age-matched controls. This observation continued stably till end of study. Body weights of diabetic rats rose gradually throughout the study, mimicking a characteristic seen in human Type II diabetes. The effect of maturation was observed in various groups when compared to Baseline group. C1 and C2 groups showed statistically significant changes in fold regulations in OCT2, PEPT2 and MATE1 and OCT2, PEPT2 and MRP2 respectively when compared to Baseline group.

The diabetic groups showed significant fold changes in OCT2, PEPT2, MATE1 and MRP2, and OCT2 and MATE1 for D1 and D2 groups respectively when compared to Baseline group. Although the effect of high fat diet-streptozotocin treatment on diabetic rats did not generate statistically significance differences in expression levels with their age-matched controls, OCT3, OAT1, OATP-3 and PGP showed 1.5 to 6 folds and 4.5 to 8 folds upregulation for D1 and D2 groups respectively.

Conclusion:
Present study offered a novel insight into the changes in gene expression levels of drug transporters expressed in rat renal PTCs under diabetic conditions. Changes in drug transporters’ expression level may affect therapeutic outcomes; therefore animal models may be developed for the study of substrate elimination for the understanding of the drug transporters’ functional characteristics.
Urinary Proteomics Of Progressive Diabetic Nephropathy

PI: Dr Lim Su Chi¹

Co-PIs: Melvin WONG¹, Wan Ching TOY², Angela MOH², Lee Ying YEoh¹, Dawn LAU², Clara TAN², Tavintharan SUBRAMANIAM¹, Chee Fang SUM¹

Affiliations: 1. Diabetes Clinic, Khoo Teck Puat Hospital, Singapore; 2. Clinical Research Unit, Khoo Teck Puat Hospital, Singapore

Introduction:
Diabetic nephropathy (DN) is the leading cause of end-stage renal disease in Singapore. The rate of progression of DN is highly variable. Risk factors predictive of DN progression are incompletely understood. Hence, there is a need to search for biomarker(s) associated with progression of DN.

Method:
In this preliminary study, we studied 2 groups (n=6) of males with type 2 diabetes: Group 1- Progressive DN (d serum creatinine≥50%) vs Group 2- Stable DN ((d serum creatinine≤10%) in a two year prospective observation cohort study. Subjects were carefully matched for potential confounders like gender, age, ethnicity and smoking status.

Urinary proteins were extracted using ethanol precipitation and subjected to de-convolution by 2D Clean Up and quantification by 2D Quant kit before pooled analysis. Using 2 dimensional fluorescence differential gel electrophoresis (2D DIGE), which employs the use of CyDye and differential labelling to allow 2 samples to be simultaneously run on the same gel. The sample was separated by 2 dimensions, 1) electrical charges then by 2) molecular weight. Wavelengths specific to the dye were used to scan the gel, generating different sample images for the same gel, which allowed the software algorithm to compare and contrast global proteome profile and individual protein concentrations. Proteins differentially up-regulated in either groups were identified by Matrix Assisted Laser Desorption/Ionization Time-of-Flight mass spectrometry and validation carried out via ELISA kit analysis in an independent male and female cohort.

Results:
DIGE analysis yielded 11 differentially excreted sports from urine and were sent for identification. One biologically relevant protein Retinol Binding Protein (RBP4) was found to be increased 1.38 fold in progressors vs stable DN.

ELISA analysis of Urinary RBP4 in an independent cohort of both males and females (progressors n=10, stable DN= 13) was 707.11±164.64 ng/mL vs 435.76±276.9 ng/mL(p= 0.002). However, this difference was abolished after adjustment for creatinine, a normalizer to control for difference in urine concentration. Urinary RBP4 correlated positively with Albumin- Creatinine Ratio (ACR) (r= 0.409, p= 0.005), serum creatinine (r= 0.411, p=0.027) and negatively correlated with estimated glomerular filtration rate (r= -0.422, p=0.023).

ELISA analysis of Plasma RBP4 of progressors vs stable DN was 57.782 ± 11.824 ug/mL vs 52.276 ± 11.083 ug/mL (p= NS) and was not significantly different.

Conclusion:
Unadjusted urinary RBP4 is able to predict progression to chronic kidney disease. However, after adjustment for creatinine, the difference was attenuated. Further studies in a larger cohort is required to re-evaluate our preliminary findings.
Association Of ACE D Allele With Acute Kidney Injury After Cardiac Surgery In An Asian Population

PI: Dr Sophia Chew
Co-PIs: Ms Roderica Ng
Affiliation: Department of Anaesthesia, Singapore General Hospital

Introduction:
Postoperative acute kidney injury (AKI) after cardiac surgery is a frequent complication with interpatient variability predicted poorly by preoperative clinical markers. 30% of local patients presenting for cardiac surgery developed AKI. Ethnicity was independently associated with the risk of AKI, with Indians and Malays having a higher risk of developing AKI after cardiac surgery. The ACE D allele has been implicated in kidney injury in African Americans and we postulate that the D allele is associated with the increased incidence of AKI in the non-Chinese after cardiac surgery.

Method:
3000 patients who underwent cardiac surgery from the 2 main heart centres from 2008 to 2012 were prospectively followed up. Preoperative blood samples were stored for DNA analysis. The primary outcome was AKI, defined using the Acute Kidney Injury Network Stage 1 criteria. The initial 1661 patients with clinical covariates and blood samples available for DNA analysis were analysed to look at risk factors between the group that develop AKI versus the group that did not. Polymerase Chain Reaction was used to detect the deletion (D) allele and insertion (I) allele of the ACE gene.

Results:
Patients with the D allele have a 23% increased risk of developing AKI after cardiac surgery (relative risk [RR]=1.228, 95% confidence interval [CI]=1.099-1.371, p<0.001). Although the frequencies of the D allele differed significantly between the 3 major ethnic groups (59.8% of Indians, 56.1% of Chinese, 49.3% of Malays) (p=0.045), the risk of developing AKI was not significantly different between them (Chinese vs Indians, RR=0.908, 95%CI=0.778-1.059, p=0.219; Malays vs Indians RR=1.025, 95%CI=0.858-1.225, p=0.784).

Conclusion:
The ACE D allele is linked to increased renal vasoconstriction and in susceptible patients, it can aggravate the problems of atheroembolism and ischaemia-reperfusion associated with cardiac surgery, leading to increased risk of AKI. However, due to the limited DNA sampling, the ACE D allele does not appear to contribute to the higher risk of AKI in the non-Chinese in our population.

References:
Comparing Toxin Removal In Hemodialysis, Hemodiafiltration, And Hemodialysis With Exercise

PI: Prof Gade Pandu Rangaiah

Co-PIs: Vaibhav Maheshwari, Titus Lau Wai Leong, Ling Lieng Hsi, Lakshminarayanan Samavedham

Affiliation: Department of Chemical and Biomolecular Engineering, National University of Singapore

Introduction:
Hemodiafiltration (HDF) has increasingly been considered as the most efficient mode of dialysis. However, long term clinical trials did not show clinically significant reduction in pre-dialysis toxin concentration when compared with high-flux hemodialysis (HD).

This is owing to the physiological resistance offered by cellular membrane or capillary endothelium. Exercise during dialysis (HD-Ex) is hypothesized to overcome this resistance and remove toxins from remote inaccessible compartments.

Method:
In the present clinical research, we compared the toxin removal outcome by high flux HD, stand-alone HDF and intra-dialytic exercise during high flux HD. Recruited patients underwent 3 dialysis sessions: (1) HD, (2) HDF, and (3) HD-Ex. Minimum one week gap was maintained between two sessions to avoid effect of any confounding factors. Dialysis prescription was same for all the three sessions. HD and HDF sessions were conducted using Fresenius 4008S and Gambro AK200 ULTRA machine, respectively. In HD-Ex, mild exercise was prescribed in three bouts of 20 min each, with 20 min gap between successive bouts. Blood samples were collected and analyzed for concentrations of urea, creatinine, and β2-microglobulin (β2M) at three time points: t = 0 min (pre-dialysis), t = 240 min (end-dialysis) and t = 360 (post-rebound). The percentage rebound is calculated to adjudge the quantum of removed toxin mass. Total of 15 subjects consented to participate, and 12 of them (7 male and 5 female) completed the 3 dialysis sessions planned for this study.

Results:
The convective volume achieved in HDF was 21.2 ± 3.7 L. The % rebound for urea is 13.3 ± 3.4 (HD), 13.6 ± 4.8 (HDF), and 13.5 ± 4 (HD-Ex); for creatinine is 22.8 ± 4.00 (HD), 22.7 ± 4.7 (HDF), and 22 ± 3.6 (HD-Ex); and for β2M is 28.5 ± 8.2 (HD), 24.1 ± 2.8 (HDF), and 27.4 ± 5.9 (HD-Ex). The results are presented as mean ± std. The % rebound results of creatinine indicate that HD-Ex performs superior to standalone HDF and HD.

For β2M, HDF is superior to both HD and HD-Ex, and HD-Ex outperforms HD. It should be noted that all the recruited patients were unconditioned to exercise and performed only mild intensity exercise (0 watt on Monark 881E). The exercise resistance was too low to elicit significant increase in toxin removal.

Conclusion:
Hence, it is concluded that prolonged HD-Ex sessions can increase the middle sized toxins removal, which can be comparable to that achieved from HDF. Further research is needed to confirm this.

References:


Early Dialysis Initiation Based On Acute Kidney Injury Network Criteria In Critically Ill Asian Patients – A Prospective Cohort

PI: Dr Lim Ciwei Cynthia
Co-PIs: CS Tan, M Kaushik, HK Tan
Affiliation: Department of Renal Medicine, Singapore General Hospital

Introduction:
Early renal support in acute kidney injury (AKI) may restore homeostasis and improve patient outcomes instead of starting dialysis as a last resort to treat refractory complications of severely impaired renal function. We aimed to compare patient mortality and renal outcome in intensive care unit (ICU) patients with AKI and renal replacement therapy (RRT) initiated based on modified Acute Kidney Network (AKIN) creatinine and urine output criteria in absence of “traditional” indications.

Method:
This was a single-center, prospective cohort study of medical and surgical ICU patients referred for AKI consecutively from 18th Dec 2010 to 27th Jan 2012 and 1st Aug 2012 to 2nd April 2013. Indications for RRT were classified as Group A: “traditional” indications including serum potassium ≥6.0 mmol/L, serum urea ≥30 mmol/L, arterial pH <7.2, serum bicarbonate <10 mmol/L, acute pulmonary edema, acute uremic encephalopathy or pericarditis; Group B: modified AKIN stage 3 without “traditional” indications; Group C: AKIN Stages 1 or 2 without “traditional” indications. Demographic, clinical and biochemical data were collected prospectively and retrospectively from patient medical records. Patients requiring RRT prior to ICU admission and those with incomplete baseline data were excluded.

Results:
One hundred and sixty nine patients were referred for AKI (mean age 59.2 ± 17.1 years; male 63.9%; diabetes mellitus 33.7%; hypertension 53.8%; ischemic heart disease 21.3%; medical ICU 72.2%; mean APACHE score 23.8 ± 6.0). Main AKI causes were sepsis (63.9%) and ischemia (34.9%). RRT was initiated in 121 patients. Complete data on RRT indications were available in 83 patients: Group A (n=26), B (n=26) and C (n=31). Those with RRT initiated in absence of “traditional” indications were examined. Comparing Group B vs. C: baseline demographics and comorbidities were similar. There were no significant differences in premorbid MDRD eGFR (p=0.36); time from ICU admission to RRT initiation (p=0.51); CRRT modality (p=0.08); average CRRT effluent flow rate (p=0.23). There was no difference in ICU mortality (33.3% vs. 33.3%, p=0.85) or in-hospital mortality (35.7% vs. 28.6%, p=0.25).

Conclusion:
In the absence of “traditional” indications, earlier RRT initiation based on AKIN criteria did not improve survival in critically ill patients. Controlled trials with well-defined dialysis criteria, including novel biomarkers, are required for further evaluation of optimal RRT timing.
Mood, Cognitive, Physical Functioning And Quality Of Life In Older Adults With Chronic Kidney Disease (CKD)

PI: A/Prof Ng Tze Pin
Affiliation: Department of Psychological Medicine, Gerontology Research Programme, Yong Loo Lin School of Medicine, National University of Singapore
Expected completion date: December 2013

Aims/Objectives:
Poor mood, cognitive and physical functioning is commonly observed in patients with end-stage renal disease and adversely impact health outcomes. However, they have seldom been investigated among older persons with dialysis-free and early stage chronic kidney disease (CKD). This research aimed to investigate (1) early stage CKD as a risk factor predicting cognitive and functional decline among older persons; (2) comorbid depression among older persons with CKD, significant risk factors predicting its presence and persistence, and its impact on quality of life outcome.

Method:
The study was conducted among participants in the Singapore Longitudinal Ageing Study (SLAS) cohort. In a prospective follow up study of community-living older persons aged 55 and above, we assessed kidney function with estimated glomerular filtration rate (eGFR) at baseline, and depression (Geriatric Depression Scale, GDS), global cognition (Mini-Mental State Examination, MMSE), instrumental activities of daily living (IADL) and SF-12 quality of life at baseline and at 2 year follow up for 1315 individuals. Cognitive decline (MMSE drop of ≥2 points) and functional decline (drop of IADL score ≥2 points) were assessed at follow up.

Results:
The prevalence of stage 3 and 4 CKD (eGFR between 15 and 60 ml/min/1.73 m2) was 18%, depression (GDS>=5) was 13%, and cognitive impairment (MMSE<=23), 15%.

In the whole sample, decreasing baseline levels of eGFR was associated with increased odds of cognitive decline at follow up: every 10 ml/min/1.73m2 decrease in eGFR was associated with an estimated 14% increased odds of cognitive decline in multivariate analyses controlling for confounding risk factors. The OR of association of CKD versus non-CKD for cognitive decline was 1.94, 95% C.I=1.23~3.05; P=0.004. Individuals with CKD were also about twice likely to show IADL decline at follow up, OR=1.99 (1.16-3.41), p=0.013.

Among 362 individuals with CKD, the presence of depression (N=42) was associated with poorer (30 percentage point difference) SF-12 QOL scores at follow up. Baseline cognitive impairment, functional disability and the presence of other chronic illnesses were significantly associated with GDS scores and depressive symptoms both at baseline and persistently at follow up. No relationship between eGFR and depressive symptoms was observed.

Comments:
This research shows that mild to moderate chronic kidney disease in older persons is a risk factor predicting cognitive and functional decline. Comorbid depression among individuals with CKD is persistent and predicts poorer quality of life. It is predicted by cognitive impairment, functional disability and the presence of other chronic illnesses, but bears no direct relationship with eGFR. Further studies with longer follow up should establish whether it also increases mortality risk. Future research should consider the development and evaluation of strategies based on targeted biomedical and psychosocial interventions to delay or prevent cognitive decline and physical disability in the elderly with early stage chronic kidney disease to improve quality of life and reduce adverse outcomes such as progression to end-stage renal disease and dialysis, hospitalizations, institutionalizations and mortality.
Targeted Inhibition Of Signal Transducer And Activator Of Transcription-3 Pathway For The Treatment Of Metastatic Renal Cell Carcinoma

PI: Dr Gautam Sethi
Affiliation: Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore
Expected completion date: December 2013

Aims/Objectives:
Renal cell carcinoma (RCC) is an adult-onset epithelial malignancy, accounting for approximately 85% of all kidney tumors with an estimated incidence of > 40,000 new cases diagnosed per year worldwide. The current treatment for advanced metastatic RCC is ineffective because of the poor prognosis and the development of resistance against molecular targeted drugs. Hence, novel agents that are safe and effective are urgently needed. Signal transducer and activator of transcription 3 (STAT3) is constitutively activated in RCC and regulates the expression of various genes that play a major role in promotion of cellular proliferation, survival, invasion and angiogenesis. Hence, STAT3 is a promising therapeutic target and blocking STAT3 signaling could lead to a potential novel therapy for metastatic RCC.

Method:
In the present report, we investigated whether zerumbone, a sesquiterpene, exerts its anticancer effect through modulation of STAT3 activation pathway. The pharmacological effect of zerumbone on STAT3 activation, associated protein kinases and phosphatase, and apoptosis was investigated using both RCC cell lines and xenograft mouse model.

Results/Expected results:
We observed that zerumbone suppressed STAT3 activation in a dose- and time-dependent manner in RCC cells. The suppression was mediated through the inhibition of activation of upstream kinases c-Src, Janus-activated kinase 1, and Janus-activated kinase 2. Pervanadate treatment reversed zerumbone-induced down-regulation of STAT3, suggesting the involvement of a tyrosine phosphatase. Indeed, we found that zerumbone induced the expression of tyrosine phosphatase SHP-1 that correlated with its ability to inhibit STAT3 activation. Interestingly, deletion of SHP-1 gene by siRNA abolished the ability of zerumbone to inhibit STAT3 activation. The inhibition of STAT3 activation by zerumbone also caused the suppression of the gene products involved in proliferation, survival, and angiogenesis. Finally, when administered i.p., zerumbone inhibited STAT3 activation in tumor tissues and the growth of human RCC xenograft tumors in athymic nu/nu mice without any side effects.

Comments:
Overall, our results suggest for the first time that zerumbone is a novel blocker of STAT3 signaling cascade and thus has an enormous potential for the treatment of RCC and other solid tumors.
Aims/Objectives:
Systemic lupus erythematosus (SLE) is a prototype systemic autoimmune disease characterized by the production of antinuclear autoantibodies. These antibodies surge in active disease and deposit in the kidney glomeruli to cause inflammation and tissue injuries. C1q deficiency is strongly associated with the generation of these autoantibodies but the underlying mechanisms are unknown.

In this study, we assess the relationship between C1q and nuclear antigens by examining C1q interaction with the nuclei during cell apoptosis.

Method:
A protocol was developed to cause cell apoptosis eventually leading to secondary necrosis and C1q binding to these cells was examined by confocal microscopy.

Results/Expected results:
C1q lacks binding to live cells but it binds progressively from the cell periphery to intranuclear structures. C1q binding to the nuclei is not ubiquitous and exhibits predominant binding to a structure resembling the nucleolus, a subnuclear domain rich in autoantigens. This has been validated through the isolation of nucleolus. The precise molecular target which C1q binds to are being identified by protein isolation and recombinant protein expression. It is also examined whether this C1q recognition of the nucleolus causes altered uptake and processing of nuclear antigens by antigen-presenting cells and impact on host tolerance of these antigens.
**T cell subset analysis:** The detection of the different T cell subsets is performed in peripheral blood by flow cytometry and in kidney biopsies by immunohistochemistry.

**Statistical analysis:** Statistical analysis will be performed using R software with the help of the Centre for Quantitative Medicine at Dukes-National University of Singapore.

**Results/Expected results:** We have observed that immunosuppression has a dramatic effect on the different T cell subsets; there is an overall decrease in numbers and frequencies of regulatory T cells, monocytes, B cells and natural killer cells in kidney transplant patients. In our preliminary analyses, we have found that kidney transplant patients with biopsy-proven acute rejection appear to have lower frequency of CD4+CD25+ regulatory T cells than patients with no rejection. Furthermore, patients with chronic rejection seem to display lower numbers of regulatory T cells when compared to patients with stable kidney transplant function. We have also detected regulatory T cells and different effector T cells in kidney tissue of patients with acute kidney transplant rejection. In coming months, we will complete the entire analysis of all the tissue and blood samples stored; expecting our final results to allow us to test our hypotheses.

**Poster Presentations**

**Minimising Renal Dysfunction In Paediatric Liver Transplant Patients With Closer Monitoring Of Renal Function And Optimising Immunosuppression Using Cylex®ImmuKnow Assay**

**PI:** A/Prof Marion M Aw  
**Affiliation:** Department of Paediatrics, National University of Singapore  
**Expected completion date:** June 2014

**Aims/Objectives:**  
1. To determine if the Cylex®ImmuKnow™ assay would be useful in helping assess adequacy of immunosuppression in paediatric liver transplant patients.  
2. To correlate the degree of immunosuppression with the incidence of graft dysfunction, as well as the incidence of post-transplant infections and other complications of over-immunosuppression.  
3. To determine if serum Cystatin C would be useful as a regular screen for renal dysfunction in our paediatric liver transplant recipients.

**Method:**  
This is a prospective study where 50 post-liver liver transplant patients on follow-up at the University Children’s Medical Institute have been recruited and consented. Blood samples (5 ml) were obtained during outpatient or inpatient visits. Relevant clinical history, immunosuppressive regimen, liver function tests were recorded. EBV PCR titers were also determined in some patients when indicated. The clinical course of the patient, including incidence of acute allograft rejection, and incidence of infections would be recorded, and these events correlated with Cylex® levels. Serum Cystatin C results will be correlated with serum creatinine results, calculated GFR (Schwartz formula) as well as creatinine clearance results obtained from annual 24-hour urine collection where possible.

**Results/Expected results:**  
Of those recruited, 46 have had at least 1 Cylex® and Cystatin-C performed. To date (31 Dec 2013), a total of 111 Cylex® tests and 63 Cystatin-C tests and creatinine tests have been processed. We expect to perform a total of at least 150 Cylex and Cystatin-C tests by the end of the study (June 2014).
Partial analysis done on 70 whole blood samples collected from 37 patients. These patients were aged 2-28 years old (mean 12 years) with a mean interval time of 5.3 years post-transplant (range 1 month–16 years) from either a living (25) or deceased (12) donor. Mean (range) cylex level was 223.95 (7-731) ng/ml. Mean (range) tacrolimus trough was 6.04 (2-13.7) ug/ml. Among those with high cylex level (n=17), 76.5% had tacrolimus trough >4ug/ml whereas among those with low cylex level (n=23), 60.9% had tacrolimus trough >4ug/ml (p=0.244). 27.2% of those with high cylex level (n=22) compared to 17.9% of those with low cylex level (n=28) had at least one episode of rejection (p > 0.05). There was no clear association between Cylex® levels and LFT or EBV PCR titres.

Analysis of Cystatin-C levels will be performed at the end of the study.

Comments:
There was no significant correlation between cylex levels, immunosuppression trough levels (therapeutic drug monitoring) and acute rejection episodes. However, children post-liver transplant with a lower net immunosuppression (i.e. higher cylex level) appeared to require higher immunosuppressive drug therapy and were at an increased risk of rejection. Measuring immunosuppressive drug levels alone may not adequately correlate with the desired biological effects of immunosuppression. The Cylex® ImmuKnow assay may have a role in monitoring the immune status of paediatric liver transplant recipients.

Portable, Non-Invasive Dry Weight Assessment And Vascular Access Monitoring Using Modern Bioimpedance Analysis For Optimal Management Of Hemodialysis Patients

PI: Dr Victor Lee Tswen Wen
Affiliation: Department of Hepatobiliary & Transplant, Singapore General Hospital Adjunct Assistant Professor, Department of Surgery, National University of Singapore

Expected completion date: June 2014

Aims/Objectives:
Presently, there is no reliable method to assess the dry weight of dialysis patients and clinical assessment is often used to assess the ultrafiltration target. This can result in overhydration or underdialysis in dialysis patients and can lead to increased morbidity and mortality. In addition, vascular access function and patency are essential for optimal management of hemodialysis (HD) patients. Low blood flow rate and loss of patency limit HD delivery extend treatment and may often result in underdialysis. Bioimpedance analysis (BIA), which is well developed in cardiovascular research, may potentially address both clinical issues related to dry weight assessment and vascular access monitoring.

The following were our main objectives and secondary objectives:

Main objectives:
1. Develop bioimpedance analysis for the accurate measurement of dry weight in dialysis patients.
2. Develop impedance plethysmography for accurate measurement of blood flow, or changes to blood flow, in the context of a small, wearable device.

Secondary objectives:
1. Develop data storage and transmission adjunct, in the context of a small, wearable device.
2. Proof-of-concept use of the developed prototype in the clinical setting for dry weight assessment and vascular access monitoring.
Method:
We have developed a wireless plaster-based bioimpedance measurement device as shown in Figure 1. This will be a low cost (<10% of current device cost) and easy to use device, which enables continuous monitoring of extracellular volume (ECV) and intracellular volume (ICV) at point of care.

The prototype plaster includes a bioimpedance measurement chip, printed antenna, and thin film battery. The bioimpedance measurement chip includes multi-frequency current source, impedance recording channel(s), and wireless transceiver. The same plaster can be used for blood flow measurement as well by adaption of the plaster with an additional recording channel (Figure 2).

Results/Expected results:
We are in the process of proof-of-concept testing in a clinical setting, and have approved Singhealth IRB (2013/597/D) dated Nov 2013. We aim to perform initial evaluation of our prototype in a clinical setting with hemodialysis patients. This is a feasible proposal as the device is non-invasive and wearable. In the context of vascular access monitoring, the device will be evaluated for its performance in the detection of difference in flow rates across different segments of vascular access in patients. The detected flow rates with our prototype will be compared with duplex ultrasound assessment and/or angiography if available. For dry weight assessment, our prototype will be placed on patient's limbs in a continuous fashion during dialysis. Changes in body volume status will be detected by our prototype as changes in bioimpedance. Serial measurements will be needed on the same patient during different dialysis sessions before and after dialysis for the evaluation of dry weight assessment, and this will be compared against current clinical evaluation of dry weight.
Augmentation Of Glutathione Levels Through Oral N-Acetylcysteine Supplementation In Type 2 Diabetic Patients To Increase Resistance To Bacterial Infection

PI: A/Prof Gan Yunn Hwen
Affiliation: Department of Biochemistry, National University of Singapore
Expected completion date: June 2014

Aims/Objectives:
Diabetes is frequently accompanied by many devastating complications including the development of diabetic nephropathy. Asians are also at higher risk of developing chronic kidney disease (CKD) as a result of diabetes. These patients are at increased risk of developing infections compared to diabetics without CKD. Melioidosis is an infectious disease where Type 2 diabetes presents as a very strong risk factor. We have previously found that immune cells from diabetic individuals with poor glycemic control were defective in controlling intracellular bacterial growth due to defective IL-12 and IFNg production. Furthermore, an altered redox balance resulting in low intracellular glutathione (GSH) to glutathione disulfide couple (GSSG) in diabetic cells is the cause for the low IL-12 production. The GSH to GSSG ratio is directly correlated with the concentration of glycated haemoglobin (HbA1c), an indication of glycemic control in diabetics. Exogenous addition of GSH or N-acetylcysteine (NAC), a precursor to the synthesis of GSH, could restore IL-12 and the microbicidal activity of monocytes and macrophages to diabetic cells. Thus, our aim is to determine whether oral supplementation with NAC in diabetic patients, an anti-oxidant widely used as a supplement and documented to be safe and well-tolerated, could help improve resistance to infection and improve disease outcome when their cells are examined ex vivo and to determine the mechanism involved. The long term goal would be to develop oral NAC supplementation as an adjunctive and preventive therapy for diabetic patients, particularly for those who are at increased risk of infection such as the ones with CKD.

Method:
1. Determine the mechanism of how increased concentrations of glutathione modulate IL-12 production.
2. Determine whether 6-week oral supplementation with N-acetylcysteine (Flumucil A) at 1200mg daily in Type 2 diabetic patients with poor glycemic control will improve resistance to bacterial infection by isolating blood from patients before and after supplementation and testing their white blood cells in vitro.

Results:
We establish that GSH directly modulates the IL-12 response of monocytes but has no effect on IFNg production from natural killer (NK) cells and monocyte bactericidal activity directly. For Type 2 diabetic patients on the NAC clinical trial, their PBMCs and subsets of immune cells showed a significant increase in free GSH concentration. However, the GSH ratio, IL-12 and IFNg production, and intracellular bacterial killing upon ex-vivo infection did not improve. Thus, oral NAC supplementation in diabetic patients is sufficient to increase intracellular GSH content in blood cells. However, modulating the free GSH content is not sufficient to improve infection outcome as it is the GSH ratio that regulates the IL-12 response in monocytes.

Comments:
Our results show that when attempting to improve an immune function directly associated with the GSH ratio, rather than overall GSH or thiol levels alone, NAC supplementation at the current dosing regimen may not be effective when the underlying source of oxidative stress is not removed. An alternative approach would be to directly trigger activation of monocytes to restore the IL-12/IFN axis during melioidosis in diabetic patients.
Activation Of Na+/K+ Atpase May Produce Protective Effects Against Kidney Injury
PI: A/Prof Bian Jinsong
Affiliation: Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore
Expected completion date: June 2014

Aims/Objectives:
To examine whether an antibody against DR region (DR-Ab) of Na+/K+ ATPase (NKA) can activate NKA activity and produce protective effects against renal injury.

Method:
Western blots were performed to examine whether the DR-Ab can bind to NKA. NKA activity was measured with a commercial kit. MTT assay was performed to examine cell viability and proliferation.

Results/Expected Results:
The binding property of DR-Ab on kidney NKA was first examined. Western blots analysis showed that DR-Ab detected NKA in kidney. DR-Ab also concentration-dependently activated kidney NKA activity. MTT assay and cell counting assays showed that DR antibody was able to induce cell proliferation in opossum kidney (OK) epithelial cells in serum free condition. This bespeaks a protective effect of DR-Ab in kidneys under malnutrition condition, which underlies renal injury and disease subsequent to lack of nutrition during fetal developmental stage. DR-Ab exerted its effects via phosphorylation of ERK/Akt pathway. Activation of NK-κB pathway may also be involved.

Comments:
Our results may imply that activation of NKA in kidney may produce protective effects against kidney injury.

A Novel Negative Feedback Loop Between MiR-196a And ANXA1 In The Regulation Of Breast And Kidney Cancer Cell Proliferation
PI: A/Prof Lina Lim Hsiu Kim
Affiliation: Department of Physiology, Yong Loo Lin School of Medicine, National University of Singapore
Expected completion date: June 2014

Aims/Objectives:
MicroRNAs (miRNAs) are endogenous ~22 nt RNAs which play critical regulatory roles in a wide range of biological and pathological processes including cancer. Up-regulation of miR-196a has been associated with cancer. However, its mechanism of action in cancer remains unclear. In our study, breast cancer and kidney cells were transfected with miR-196a or empty vector to investigate the role of miR-196a in cell proliferation, migration and invasion, and drug-sensitivity.

Method:
Transfection, proliferation assays (counting, cell titre), migration assays (wound healing, chemotaxis), apoptosis assays.

Results/Expected Results:
Ectopic miR-196a expression in vitro significantly enhanced cell proliferation in both breast cancer cell lines. It also enhanced cell migration and invasion, and positively affected drug-sensitivity to the chemotherapeutic drug, Etoposide. A reverse correlation between miR-196a and annexin-1 (ANXA1) expression and another novel predicted target, ZYMND11 was noted in breast cancer cell lines, indicating that ANXA1 and ZYMND11 may be targets of this microRNA. MiR-196a reduced ANXA1 and ZYMND11 expression at both mRNA and protein level, and inhibited their expression by targeting the binding site in the 3'-untranslated region (3'-UTR). The ANXA1 –mediated repression in cell proliferation was reversed by miR-196a over-expression. Interestingly, we also found that ANXA1 could inhibit the expression level of primary, precursor and mature miR-196a, suggesting ANXA1 might inhibit the transcription of this microRNA.

Comments:
In conclusion, we report a novel negative feedback loop between miR-196a and ANXA1, where ANXA1, a target of miR196a, also inhibits the transcription of miR-196a.
Recurrent 11q22 Focal Amplification In Sarcomatoid Chromophobe Renal Cell Carcinoma Point Towards Its Involvement In Sarcomatoid Transformation

**PI:** Dr Huang Dachuan  
**Affiliation:** Division of Medical Science, National Cancer Centre Singapore  
**Expected completion date:** June 2014

**Aims/Objectives:**  
Most chromophobe renal cell carcinomas are low stage, cured by surgery and have a relatively good prognosis. Losses of chromosomes 1, 2, 6, 10 and 17 are frequent genetic abnormalities in both classic and eosinophilic chromophobe renal cell carcinomas. Chromophobe renal cell carcinomas with distant metastases or sarcomatoid transformation are uncommon and little is known about their chromosomal abnormalities. Most have been reported as single cases and few cytogenetic data are available. Therefore, we sought to identify cytogenetic characteristics and the functional consequences in sarcomatoid and metastatic chromophobe renal cell carcinomas.

**Method:**  
In order to address these questions, we integrated the single nucleotide polymorphism (SNP) array data and the gene expression profiling (GEP) data from 12 cases of sarcomatoid renal cell carcinomas.

**Results/Expected Results:**  
We identified a chromophobe RCC patient with sarcomatoid features that showed a profound focal amplification in the 11q22 locus. GEP analysis showed that many of the genes in this locus play a role in EMT, invasion and metastasis. In particular, YAP1 together with other metalloproteinase genes have been shown to be very potent transforming oncogenes.

**Comments:**  
According to our knowledge, this is the second case of sarcomatoid renal cell carcinoma with 11q22 amplification reported.

Future work will involve establishing the role of 11q22 in sarcomatoid transformation through analysis of mixed carcinomatous/sarcomatoid RCC, as well as by perturbing 11q22 member expression in functional studies.

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Quality Of Life And Psychosocial Outcomes Of Living Kidney Donation In Singapore

**PI:** Dr Terence Kee  
**Affiliation:** Department of Renal Medicine, Singapore General Hospital  
**Expected completion date:** June 2014

**Aims/Objectives:**  
Health-related quality of life (HRQOL) and psychosocial outcomes is a key concern among living kidney donors (LKD). We sought to determine the HRQOL and psychosocial outcomes of LKD and compared it to the general public in Singapore.

**Method:**  
We conducted a cross-sectional survey of LKD and the general public from June 2012 to January 2013. Instruments used included Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Body Image States Scale (BISS), Rosenberg Self-esteem Scale (RSES), Short Form Health Survey (SF-36), and study-specific questionnaire that captured information on perceptions on living organ donation.

**Results/Expected Results:**  
A total of 139 LKD (mean age = 53.6 years) and 380 general public participants (mean age = 41.2 years) were recruited. LKD had lower level of education level (P<0.001) and lower monthly household income (P=0.042) than the general public. The norm-based HRQOL scores of all domains in LKD and general public were comparable (all P>0.05). There were no significant differences in psychosocial outcomes where anxiety, depression, body-image and self-esteem statuses were concerned (P>0.05). Both groups reported ‘very low anxiety’, with reported moods in the ‘normal range’, and so were their self-esteem and body image statuses.

Hence it would be interesting to study a large cohort of lupus patients to determine the relationship between treatment response and specific BIM genotypes.

**Comments:**  
Even though the LKD were older, less educated and had low income, their norm-based HRQOL across all domains were not significantly different from the general public. There was no evidence of lower HRQOL scores and poorer psychosocial outcomes in the LKD.
PROJECTS FUNDED BY THE VENERABLE YEN PEI-NKF RESEARCH FUND
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

Introduction:
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 were presented to rheumatologists and renal physicians to score with a rating of 0 (no activity) to 3 (severe activity). These scenarios included clinical data, medications, renal function tests, urinalysis and kidney biopsy results (if available). 160 scenarios were created through retrospective review of patients case sheets and uploaded to a web-based survey platform.

Aim 2: LN patients with a 10 year follow up had 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 were presented to rheumatologists and renal physicians to be scored and comparison of agreement between the rating and the calculated scores obtained using established indices were carried out using the chance-adjusted measure of agreement.

Results/Expected Results:
Scoring of case scenarios has been completed and analysis is underway. 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.
ONGOING RESEARCH PROJECTS

BASIC SCIENCE

*The Complement Protein C1q Recognizes Defined Subnuclear Regions In Apoptotic Cells
Lu Jinhua
Department of Microbiology, Yong Loo Lin School of Medicine
National University of Singapore

*A Novel Negative Feedback Loop Between Mir-196a And ANXA1 In The Regulation Of Breast And Kidney Cancer Cell Proliferation
Lina Lim Hsiu Kim
Department of Physiology, Yong Loo Lin School of Medicine
National University of Singapore

*Recurrent 11q22 Focal Amplification In Sarcomatoid Chromophobe Renal Cell Carcinoma Point Towards Its Involvement In Sarcomatoid Transformation
Huang Dachuan
Division of Medical Science
National Cancer Centre Singapore

Assessment Of Autophagy In Renal Cells Under Diabetic Conditions
Li Guodong
Department of Clinical Research
Singapore General Hospital

Interleukin-27 As A Crucial Accessory Mediator In The Pathogenesis Of Pediatric Minimal Change Nephrotic Syndrome
Yeo Wee Song
Department of Paediatrics
National University Health System

Identification Of Endogenous Regulators Of Kidney Aquaporins
Sugunavathi Sepramaniam
Department of Biochemistry, Yong Loo Lin School of Medicine
National University of Singapore

CLINICAL RESEARCH

*Mood, Cognitive, Physical Functioning And Quality Of Life In Older Adults With Chronic Kidney Disease (CKD)
Ng Tze Pin
Department of Psychological Medicine, Gerontology Research Programme,
Yong Loo Lin School of Medicine
National University of Singapore

*Minimising Renal Dysfunction In Paediatric Liver Transplant Patients With Closer Monitoring Of Renal Function And Optimising Immunosuppression Using Cylex®Immuknow Assay
Marion Aw
Department of Paediatrics
National University of Singapore

*Augmentation of glutathione levels through oral N-acetylcysteine supplementation in Type 2 diabetic patients to increase resistance to bacterial infection.
Gan Yunn Hwen
Department of Biochemistry
National University of Singapore

*Quality Of Life And Psychosocial Outcomes Of Living Kidney Donation In Singapore
Terence Kee
Department of Renal Medicine
Singapore General Hospital

Prospective Monitoring Of Volume And Nutritional Status Using Bioimpedance Spectroscopy In Incident Peritoneal Dialysis Patients And Prospective Monitoring Of Fluids Status During Episodes Of Volume Overload In Prevalent Patients
Marjorie Foo
Department of Renal Medicine
Singapore General Hospital

Reducing Nephrotoxicity Of Vancomycin: A Prospective, Randomized Study Of Continuous Versus Intermittent Infusion Of Vancomycin.
Jolene Oon
Division of Infectious Disease, Department of Medicine
National University Hospital
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Singapore Vascular Access Outcomes Study: A Prospective Longitudinal Study
Jackie Ho Pei
Department of Cardiac, Thoracic and Vascular Surgery, National University Hospital; Department of Surgery, Yong Loo Lin School of Medicine, National University of Singapore

The Effectiveness Of Self-Efficacy Psychoeducational Intervention To Enhance Outcomes Of Patients With End Stage Renal Disease: A Randomised Controlled Trial
He Hong-Gu
Alice Lee Centre for Nursing Studies, Yong Loo Lin School of Medicine, National University of Singapore

TRANSLATIONAL RESEARCH

*Targeted Inhibition Of Signal Transducer And Activator Of Transcription-3 Pathway For The Treatment Of Metastatic Renal Cell Carcinoma
Gautam Sethi
Department of Pharmacology, Yong Loo Lin School of Medicine
National University of Singapore

*Phenotypic And Functional Analysis Of CD39+ Regulatory T Cells (Tregs) In Kidney Transplant Patients, And Their Correlation With Clinical Outcomes
Francisco Salcido-Ochoa
Department of Renal Medicine, Singapore General Hospital

*Portable, Non-Invasive Dry Weight Assessment And Vascular Access Monitoring Using Modern Bioimpedance Analysis For Optimal Management Of Hemodialysis Patients
Victor Lee Tswen Wen
Department of Surgery, National University of Singapore

*Activation Of Na+/K+ Atpase May Produce Protective Effects Against Kidney Injury
Bian Jinsong
Department of Pharmacology, Yong Loo Lin School of Medicine
National University of Singapore

*Cool Vs. Warm Dialysate: Comparing The Toxin Removal Outcome
Gade Pandu Rangaiah
Department of Chemical and Biomolecular Engineering
National University of Singapore

Thermo-Responsive Magnetic Nanoparticles For Combined Modalities Of Kidney Cancer
Lee Chee Wee
School of Applied Science, Temasek Polytechnic

Biomarkers To Predict Tenofovir Related Renal Toxicity
Lawrence Lee Soon-U
Investigational Medicine Unit
National University of Singapore

Calcijek® Supplementation & Vitamin D In Mediating Susceptibility To Fungal Infection
Louis Chai
Division of Infectious Diseases, Department of Medicine
National University Health System

The Predictive Value Of Immune And Genetic Markers In Lupus Nephritis
Lian Tsui Yee
Department of Rheumatology, Allergy and Immunology
Tan Tock Seng Hospital

Improving Outcomes In Patients With Coexisting Multimorbid Conditions – The Development And Evaluation Of The Combined Diabetes And Renal Control Trial (C-DIRECT)
Konstadina Griva
Department of Psychology, National University of Singapore

Role Of Angiomotin In The Pathogenesis Of Membranous Nephropathy
Isaac Liu Desheng
Department of Pediatrics, National University Health System

*Presented as a poster
Aims/Objectives:
Diabetes is the major risk factor leading to kidney dysfunction and failure, being the principal cause for kidney dialysis in Singapore. In the development of diabetic nephropathy, hyperglycemia and dyslipidemia induce damages on renal cells, called as glucotoxicity and lipotoxicity respectively. Glucotoxicity and lipotoxicity may stimulate or inhibit a host of signaling pathways in the cell stress to produce the adverse effects including abnormal cell proliferation, change in cell permeability, and apoptotic cell death. Autophagy is a cellular process which senses cell stresses and degrades cellular components for energy needs and to promote cell survival. Autophagy plays an important role in development, aging, lipid metabolism and immunity, and is also involved in the pathophysiology of many diseases such as diabetes and cancers. Little information is available on the possible implication of autophagy in the pathogenesis of diabetic nephropathy. This abstract mainly reports the work on assessing the participation of autophagy in the damage of renal cells due to lipotoxicity.

Method:
Human renal epithelial cell line (RC-124) was cultured with control or high levels of free fatty acids [a mixture of oleate and palmitate, 2:1 (w/w)] for different periods. Afterwards, the cells were harvested for homogenates and autophagy was assessed by western blotting using antibody against LC3-II, an indicator of autophagy activation.

Results/Expected results:
RC-124 cells displayed morphological changes after exposure to high fatty acids (0.5-1 mM). Cells lost their normal shiny and smooth surface which became jagged and coarse. An increase in LC3-II occurred as early as 4 hrs after treatment with high fatty acids and the effect lasted at least for 24 hrs.

Comments:
High free fatty acids can lead to induction of autophagy in kidney epithelial cells. Dyslipidemia in diabetes may induce autophagy in renal cells which could contribute to the development of diabetes-related kidney complications.
**Interleukin-27 As A Crucial Accessory Mediator In The Pathogenesis Of Pediatric Minimal Change Nephrotic Syndrome**

**PI:** Dr Yeo Wee Song  
**Affiliation:** Department of Paediatrics, National University Health System  
**Expected completion date:** June 2016

**Aims/Objectives:**

Minimal change nephrotic syndrome (MCNS) is the commonest cause of childhood nephrotic syndrome in Singapore. 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 previously demonstrated that interleukin-13 (IL-13) expression was upregulated in CD4+ and CD8+ T-cells of children with MCNS in relapse and 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 gene expression, leading to increased vav1 gene expression, which was associated with elevated level of activated Rho, and subsequent actin cytoskeleton rearrangement. 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. As IL-13 is a known modulator of monocyte function, we went on to elucidate the molecular and genetic signature of unstimulated monocytes obtained from paired pediatric MCNS patient samples which demonstrated an upregulation of IL-27, a known inducer of c-maf which is a crucial factor in Th2 polarization, in relapse compared to remission. Plasma IL-27 levels were also significantly increased in MCNS in relapse compared to remission. The study aimed to delineate the role of IL-27 in the pathogenesis of MCNS.

**Method:**

Conditionally immortalized human podocyte cell line AB8/13 was cultured on type I collagen-coated cell culture dish (Iwaki, Japan) in complete medium (RPMI 1640 medium containing L-glutamine (GIBCO; Invitrogen, USA), 10% heated inactivated fetal bovine serum (GIBCO; Invitrogen, USA), 100units/ml penicillin-streptomycin (GIBCO; Invitrogen, USA), and 1% insulin-transferrin-selenium supplement (GIBCO; Invitrogen, USA)). The cells were grown at a permissive temperature of 33°C with 5% CO2. Cells were passaged upon reaching 90% confluency and differentiated for 10 to 14 days at 37°C and 5% CO2. Fully differentiated cells were incubated with IL-27 (20ng/ml) (R&D systems, USA), LPS (positive control) or culture medium alone (negative control; unstimulated podocytes). The podocytes were then harvested for actin cytoskeleton characterization and analysis of gene expression.

**Results/Expected results:**

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. This was observed as soon as 4 hours after incubation with IL-27. The findings of decreased podocin, nephrin and dystroglycan expression were similar to those observed in glomeruli isolated from MCNS patients. Incubation of IL-27 demonstrated cytoskeleton rearrangements similar to LPS-treated podocytes, suggesting a highly plausible role of IL-27 in the pathogenesis of MCNS.

**Comments:**

The above preliminary results suggest IL-27 as a highly plausible crucial accessory mediator in the pathogenesis of MCNS, in addition to IL-13. Further mechanistic studies, are however, required to delineate its exact role in the pathogenesis of MCNS.
Identification Of Endogenous Regulators Of Kidney Aquaporins

**PI:** Dr Sugunavathi Sepramaniam  
**Affiliation:** Department of Biochemistry, Yong Loo Lin School of Medicine, National University of Singapore  
**Expected completion date:** June 2016

**Aims/Objectives:**
Diabetes mellitus (DM) is a common endocrine disease that has become a global pandemic affecting almost 346 million people worldwide. DM is the main cause of end-stage renal disease (ESRD), accounting for approximately 44% of the new cases annually. At the advanced stage, manifestation of diabetic nephropathy is characterized by large amounts of proteinuria and fluid retention in the body. The exact cause of diabetic nephropathy remains largely unknown and the mechanisms underlying altered renal tubular reabsorption of water and sodium in response to glomerular hyper-filtration are also not clear. Regulation of body water by the kidneys is mainly controlled by aquaporins. The kidney expresses eight isoforms of aquaporins implicating their functional importance in kidney physiology. Although the functional roles are well studied for aquaporins 1, 2, 3 and 4, the roles of aquaporins 6, 7, 8 and 11 are relatively unknown. Yet alterations in these molecules have been associated with renal complications such as Nephrogenic Diabetes Insipidus, polyuria and diabetic nephropathy. Thus, regulating these aquaporins might prove beneficial in disease conditions. We propose to identify microRNAs (endogenous regulators of gene expression) that regulate the expression of kidney aquaporins. Identification of microRNA based regulators for aquaporins will allow us to study the functional roles of these molecules in kidney physiology and potentially modulate the expression of these molecules.

**Method:**
Bioinformatics target predictions for aquaporin genes were performed using various microRNA databases. Profiling of kidney cell lines was performed to identify endogenously expressed microRNAs. Aquaporin genes were amplified and cloned into reporter constructs for interaction studies.

**Results/Expected results:**
In silico analyses highlighted the presence of large range of microRNAs with the potential to target and regulate the expression of kidney aquaporins. This data was verified with the list of endogenously expressed microRNAs to identify the crucial microRNAs expressed in kidney cell lines. The aquaporin 1 3’UTR was amplified and cloned into a luciferase reporter construct for microRNA target interaction studies. miR-146a, miR-320a, and miR-103 were identified as potential regulators of aquaporin 1, with miR-146a being the strongest regulator.

**Comments:**
Identifying microRNA based regulators for aquaporins will have potential therapeutic implications with regard to kidney diseases. These regulators can be further used to study and understand the molecular pathology involved.
CLINICAL RESEARCH

Prospective Monitoring Of Volume And Nutritional Status Using Biomimpedance Spectroscopy In Incident Peritoneal Dialysis Patients And Prospective Monitoring Of Fluids Status During Episodes Of Volume Overload In Prevalent Patients

PI: Dr Marjorie Foo
Affiliation: Department of Renal Medicine, Singapore General Hospital
Expected completion date: June 2014

Aims/Objectives:
Overhydration and malnutrition are independent predictors of morbidity and mortality in peritoneal dialysis (PD). The accurate assessment of fluid status and body composition in PD patients remains a challenge. The clinical surrogate marker for fluid status, i.e. blood pressure, does not correlate in totality, however, the determination of body fluid volumes via bioimpedance methods based on assumptions that low frequency electric current flows exclusively in the extracellular water (ECW) and high frequency current passes through total body water, has been shown to be consistent in predicting ECW. Apart from ECW and total body water (TBW) assessment, these measurements which are objective can be used to infer intracellular water (ICW) and hence body composition. Bioimpedance spectroscopy when used concomitantly with clinical assessment may help to improve diagnosis accuracy of hydration and nutrition status.

The assessment of nutrition in dialysis is complicated due to fluid changes impacting on real weight gain from lean body mass (LBM) and calories from dialysate. Protein caloric malnutrition (PCM) is the main form of malnutrition in PD accounting for half of incident patient starting dialysis. This usually arises from late start dialysis or after an episode of PD peritonitis. Assessment of improve nutrition is usually via better fluid control and rise in serum albumin while LBM is through anthropometric measures of triceps thickness and subjective improvement in overall functionality. Body composition measurement using body composition monitor (BCM) will provide an assessment which is rapid, objective and reproducible.

The outcome is aimed to tailor diagnosis and hence management in an efficient manner.

Method:
Prospective longitudinal study aimed at comparing assessment of nutritional status using BCM versus subjective global assessment (SGA) by dietitian and assessment of fluid status using BCM versus clinical assessment by clinician based on hemodynamic parameters i.e. BP, weight and oedema etc.

Fluid overload protocol: incident patient
Patient will be recruited at the end of training. Fluid status will be established via BCM and clinician assessment. On subsequent follow up at month 1.5, 3, 6,9,12, similar assessment will be performed. Routine blood test will be performed as per usual clinic visit requirement.

Fluid overload protocol: prevalent patient
Patients admitted with diagnosis of overhydration that needed rapid exchange for excess ultrafiltration will be subjected to regular BCM for comparison with clinician assessment of fluid status. Daily weights and fluid balance will be collected for analysis. Physicians’ assessment will be blinded for the period of the study.

Nutritional monitoring
All incident patients will be assessed by dietitian using traditional SGA scoring and comparison will be made with BCM assessment of nutritional status of LBM and fat mass. The prospective monitoring will be performed at each visit on months 1.5, 3, 6 and 12. Surrogate markers of nutrition e.g. serum albumin, haemoglobin, bone profile and renal panel will be taken as part of the usual clinic visit requirements.

Results/Expected results:
The study is ongoing. Analysis of BCM vs. clinical assessment will be done using paired T test. Longitudinal assessment will be analysed using multivariate and Cox regression using SPSS.
Reducing Nephrotoxicity Of Vancomycin: A Prospective, Randomized Study Of Continuous Versus Intermittent Infusion Of Vancomycin

**PI:** Dr Jolene Oon  
**Affiliation:** Division of Infectious Disease, Department of Medicine, National University Hospital  
**Expected completion date:** June 2014

**Aims/Objectives:**
1. Compare the rate of nephrotoxicity due to vancomycin given by different modes  
2. Compare the clinical efficacy of vancomycin  
3. Determine the population pharmacokinetics of vancomycin in local patients

**Method:**  
A prospective multicenter randomized controlled study comparing vancomycin given as continuous infusion or intermittent infusion is proposed. Patients will be enrolled from a diverse ethnic population from various outpatient antimicrobial parenteral sites in Singapore. Nephrotoxicity defined as acute kidney injury will be used as the primary endpoint of the study. We plan to recruit 110 patients in each group over a period of 2-3 years. Eligible patients are those with stable and normal baseline renal function requiring at last >10 days vancomycin for documented infections.

**Results/Expected results:**  
The primary outcome will be nephrotoxicity as defined by the Acute Kidney Injury Network (AKIN) criteria. The secondary outcome will be the pharmacokinetics of vancomycin and the biomarkers in detecting early nephrotoxicity. These include serum and urine NGAL and serum and urine cystatin C.

**Comments:**  
Recruitment of patients are currently ongoing.

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BIM Genotypes In Patients With Lupus Nephritis: Associations With Lupus Pathogenesis And Treatment Response

**PI:** Prof Fong Kok Yong  
**Affiliation:** Department of Rheumatology and Immunology, Singapore General Hospital  
**Expected completion date:** June 2014

**Aims/Objectives:**  
Lupus nephritis is common among local lupus patients and some have treatment resistant diseases. The current study aims to firstly compare the prevalence of the BIM genotypes among a large cohort of lupus patients and normal individuals and to determine whether specific BIM genotype is associated with corticosteroid treatment resistance.

**Method:**  
300 patients and 100 normal controls will be studied. The BIM genotype will be assayed by PCR methodology. The clinical data and autoantibodies profiles will be abstracted by chart review with the cumulative corticosteroids dosage from onset of nephritis to remission calculated, and documentation of steroid sparer and/or cytotoxics use. Specific genotypes will be correlated with cumulative corticosteroid dosage. Disease activity and permanent organ damage will be scored using SLEDAI and SLICC Damage Index. Prevalence of the BIM (wild) and BIM (poly) will be calculated and the genetic data will be assessed using the Hardy-Weinberg equilibrium.

**Results/Expected Results:**  
A pilot study of 5 lupus patients done previously showed the following:

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<tr>
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<th>BIM (Poly)</th>
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<tr>
<td>Oral Prednisolone</td>
<td>7,336 mg</td>
<td>6,563 mg</td>
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<tr>
<td>Oral Azathioprine</td>
<td>YES</td>
<td>YES</td>
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<tr>
<td>IV CYC or Oral MMF*</td>
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* IV CYC or MMF refers to IV cyclophosphamide and mycophenolate mofetil
The mean cumulative prednisolone dosages per patient within the 1 year post biopsy period was 12% higher in the BIM (Wild) group compared to BIM (Poly) group.

Hence it would be interesting to study a large cohort of lupus patients to determine the relationship between treatment response and specific BIM genotypes.

Comments:
We have recruited 202 patients and 101 normal controls, the recruitment and analysis of data are in progress.

---

**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, Singapore  
**Expected completion date:** Jun 2014

**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. We aim to

1. Determine the distribution of ISN/RPS classes in comparison to that by the WHO classification in a local cohort of LN patients
2. Do comparison studies to determine agreement among pathologists of the ISN/RPS classification system
3. Determine the influence of ISN/RPS class and other histological features on renal and survival outcome of LN

**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, excluding biopsy specimens that do not have 10 or more non-sclerotic glomeruli.

Renal histopathological specimens of LN patients will be reviewed and reclassified according to the ISN/RPS 2003 classification. A scoring form will be used to record the ISN/RPS classification, activity and chronicity index. Comparison of the ISN/RPS classification with those in the previous pathology reports will be done. In the case of significant divergence between the previous and the ISN/RPS classification, the assessment
will be repeated. Important electron microscopy or immunofluorescence findings available from the reports will be included in the classification. Where there are repeat biopsies, the earlier biopsy will serve as the reference for the subsequent biopsy. Intraclass correlation coefficients (ICCs) will be calculated. Data on clinical and laboratory parameters recorded in the study database, as well as extracted from case records will be included in the analysis with the histopathological data (ISN/RPS classification and other histological features) 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:
To be determined

Comments:
To be determined
Conclusion:
Stenting, particularly with graft placement for cephalic arch stenosis seems significantly better at improving primary patency compared to angioplasty alone at 6 months. However, as the sample size is still small and patients were not equally allocated to 3 treatment arms, comparisons between the DES and SG groups and subgroup analysis for restenosis rates are limited at this stage. Further patient recruitment is expected to provide this information, and potentially change the standard of care for this group of patients at our institution.

Clinical Prevalence And Associated Factors Of Erectile Dysfunction In Uremia
PI: Prof P Ganesan Adaikan
Affiliation: Department of Obstetrics and Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore
Expected completion date: December 2014

Aims/Objectives:
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. In Singapore, where there is considerable number of patients undergoing chronic dialysis therapy, limited epidemiologic and community data exists on the prevalence, severity and clinical correlates of ED. 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.

Results:
To date, 150 uremia patients have been evaluated and the project is expected to be completed with an additional 50 patients before the full analysis of the project data is carried out. Observational findings from this study have indicated that up to 65% of the uremia patients were not sexually active for at least the past 4 weeks because of underlying erectile difficulties. Severe ED (IIEF score: 0-6) was noted in 66.7% of the uremia patients in contrast to only 6% reporting normal erectile function (IIEF score: 25-30). In general, 30% of the uremia patients had low desire for sexual activity (IIEF score 0-2).
Comments:
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. Further analysis of the data is expected to identify the causes for the severity of ED in this group. This study is also likely to provide clinical correlates on the social, psychological, treatment-related (drugs) and comorbid factors for the sexual quality of life in these patients and for further interventional approaches.

Usefulness Of Ngal As A Biochemical Marker For Acute Kidney Injury In Patients With Sepsis And Cardiac Failure

PI: Dr Jeremy Wee Choon Peng
Affiliation: Department of Emergency Medicine, Singapore General Hospital
Expected completion date: December 2014

Aims/Objectives:
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).

Method:
Patients presenting to the ED, meeting the inclusion criteria will be recruited in the trial. NGAL levels will be tested using serum samples obtained at the same venipuncture as with routine blood investigations which include serum creatinine.

Patients must meet all of the following inclusion criteria to be eligible for enrolment into the trial:

1. Age more than 21 years old
2. eGFR of 60 mL/min/1.73m2 calculated via 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) OR
      i. Temperature greater than 38 degrees Celsius or less than 36 degrees Celsius
      ii. Respiratory rate greater than 20 breaths per minute or a PaCO2 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/mm3 or less than 4 000 cells/mm3 or greater than 10% immature forms
   c. Require hospital admission.
The presence of any of the following will exclude a patient from study enrolment:

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

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

Results/Expected results:
The serum levels of 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.

If NGAL is 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.

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: December 2014

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 within 2 years post-transplant while controls will include those who did not develop NODAT after a minimum follow-up of 2 years 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 the 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 CNI disposition.

Results/Expected Results:
This study is currently ongoing. The effort will contribute information on genetic risk factors for NODAT that could explain differences in predisposition to CNI-associated NODAT among renal transplant recipients.

Comments:
Findings from this study will provide insight into possible genetic predisposition for CNI-associated NODAT in 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.
Aims/Objectives:
Clinical practice guidelines recommend different blood pressure (BP) goals for chronic kidney disease (CKD) patients. Previous studies have shown poor attainment of BP targets in treated patients. However, excessively low BP is associated with increased mortality, especially in the elderly. The profile of BP management in Asian CKD patients is unclear. We assessed the BP and anti-hypertensive medication profile in a multi-ethnic Asian stable CKD population.

Method:
We prospectively recruited 613 stable CKD outpatients. Target blood pressures (BP, mm Hg) were categorized into four groups based on the Mean Arterial Pressures (MAP =1/3 systolic blood pressure + 2/3 diastolic blood pressure) of <140/90, <130/80, <125/75 and <100/60. The number of anti-hypertensive medications each patient consumed was recorded. ANOVA was used to compare means of BP by number of BP medications.

Results/Expected Results:
Patients (423/613) with a history of hypertension, have a higher mean MAP compared to those without (97±12 vs. 92±12, p <0.001). About 45% of patients had a MAP >97 mm Hg, and 39.6% of patients had a MAP <92 mmHg (Table 1). On average, each patient is on 2 anti-hypertensive medications. Mean BP were similar regardless of the number of medications taken (Table 2).

<table>
<thead>
<tr>
<th>Blood Pressure Goals (mm Hg)</th>
<th>Mean Arterial Pressure targets (MAP, mm Hg)</th>
<th>Number of patients (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;140/90</td>
<td>107</td>
<td>523 (85.3)</td>
</tr>
<tr>
<td>&lt;130/80</td>
<td>97</td>
<td>338 (55.1)</td>
</tr>
<tr>
<td>&lt;125/75</td>
<td>92</td>
<td>243 (39.6)</td>
</tr>
<tr>
<td>&lt;100/60</td>
<td>73</td>
<td>19 (3.1)</td>
</tr>
</tbody>
</table>

Comments:
In practice, the safest BP target would be between a MAP of 92 to 97 mm Hg. A large proportion of CKD patients (45%) did not achieve target MAP, but also a significant percentage (39.6%) of patients may have increased risks of mortality with MAP <92 mm Hg.
Aims/Objectives:
Chronic kidney disease (CKD) is a common health problem frequently complicated by hypertension. Previous studies of the general population showed an association of body composition (percentage body fat, %BF; body mass index, BMI; waist-hip ratio, WHR) with the components of blood pressure (BP; systolic BP, SBP; diastolic BP, DBP). This is unclear in stable Asian CKD patients. We assessed the association of these parameters with blood pressure in a multi-ethnic Asian CKD population.

Method:
We recruited 115 stable CKD patients (n=115, 74.8%), and measured SBP and DBP, according to clinical practice guidelines using Dinamap, GE HealthCare. Anthropometry was performed and body composition determined with multi-frequency bioimpedance (Bodystat Quadscan 4000). Non-normal data (BMI, WHR, %BF) were natural log-transformed for statistical analyses.

Results/Expected Results:
There are no significant differences between Chinese and non-Chinese patients (Table 1). When classified according to BMI, there is an association with being overweight and SBP (p=0.05) (Table 2). In this study population, SBP was not associated with %BF (p=0.059), BMI (p=0.64) and WHR (p=0.86). DBP was also not significantly associated with %BF (p=0.11), BMI (p=0.99) and WHR (p=0.61).

Table 1. Characteristics of participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>All (n=115)</th>
<th>Non-Chinese (n=29)</th>
<th>Chinese (n=86)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60 ± 13</td>
<td>61 ± 11.88</td>
<td>57 ± 14.4</td>
<td>0.17</td>
</tr>
<tr>
<td>%BF</td>
<td>31.1 (23.4 – 39.2)</td>
<td>31 (23.38 – 38.6)</td>
<td>33 (23.5 – 41.5)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Data are mean ± SD for variables normally distributed, or median (25%-75%) for those non-normally distributed.

Table 2. Associations between BMI and BP

<table>
<thead>
<tr>
<th>BMI (kg/m2)</th>
<th>Normal (n=28)</th>
<th>Overweight (n=45)</th>
<th>Obese (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (&lt;23)</td>
<td>26.5 (23 – 29.5)</td>
<td>26 (22.8 – 28.2)</td>
<td>28 (24.15 – 30.8)</td>
</tr>
<tr>
<td>Overweight (≥23 to &lt;27)</td>
<td>0.91 (0.87 – 0.96)</td>
<td>1 (0.87 – 0.97)</td>
<td>1 (0.87 – 0.96)</td>
</tr>
<tr>
<td>Obese (≥27)</td>
<td>137 ± 18</td>
<td>137 ± 19</td>
<td>137 ± 15</td>
</tr>
</tbody>
</table>

Data are mean ± SD for variables normally distributed, or median (25%-75%) for those non-normally distributed.

Comments:
Multi-frequency bioimpedance determined percentage body fat is not associated with blood pressure in stable chronic kidney disease patients. The lack of statistical significance in this association between body composition and BP may be confounded by antihypertensive medication use. Research using a larger population sample may allow greater understanding of the effects of body composition on BP in CKD patients.
Blood Pressures And Plasma B-Type Natriuretic Peptide Levels In A Multi-Ethnic Asian Population Of Stable Chronic Kidney Patients
PI: Dr Teo Boon Wee
Affiliation: Department of Medicine, National University Health System
Expected completion date: December 2014

Aims/Objectives:
Stable chronic kidney disease (CKD) patients retain sodium and water which increases intravascular fluid volume, leading to myocardial stretching and release of B-type natriuretic peptide (BNP). The profile of BNP levels with blood pressures in Asian CKD patients is unclear. We assessed the association of serum BNP levels with blood pressures in a multiethnic-Asian population of stable CKD patients.

Method:
We prospectively recruited stable CKD patient and performed anthropometry, office blood pressure measurements (Dinamap) according to practice guidelines, and venepuncture. Blood samples were assayed for BNP (Abbott), and creatinine to estimate glomerular filtration rate (eGFR) with the CKD-EPI equation. Data are reported as mean±SD or median and interquartile range where appropriate. Non-normally distributed data were natural log-transformed for analyses. Correlation and linear regression were used to assess associations.

Results/Expected results:
There were 613 patients (male 55.1%, Chinese 74.7%, Indian 6.4%, Malay 11.4%, Others 7.5%) with mean age 57.8±14.5 years, comprising of 35.7% diabetics, and 69% hypertensives. Means: systolic blood pressure (SBP) 139±21mmHg, diastolic blood pressure (DBP) 75±11mmHg, serum creatinine 165±115µmol/L, estimated GFR 53±32mL/min/1.73m², and plasma BNP median 29pg/L (IQR:13-74). Log BNP was higher in women (3.67±1.07 vs. 3.42±1.17), diabetics (3.91±1.17 vs. 3.32±1.06), and hypertensives (3.65±1.15 vs. 3.26±1.03). Log BNP is positively correlated with SBP (r = 0.33, p <0.001), but negatively correlated with log eGFR (r = -0.49, p <0.001), and DBP (r = -0.13, p <0.001).

Comments:
Higher SBP are associated with high BNP level, whereas higher DBP are associated with lower BNP levels.

Association Of Bioimpedance Spectroscopy-Determined Parameters Of Water Distribution With Systolic Blood Pressure
PI: Dr Teo Boon Wee
Affiliation: Department of Medicine, National University Health System
Expected completion date: December 2014

Aims/Objectives:
Chronic kidney disease (CKD) patients frequently have fluid overload associated with hypertension. Previous studies of bioimpedance analysis of water distribution in CKD patients were hampered by the lack of CKD patients in the development of empirical prediction equations. Bioimpedance spectroscopy offers more accurate assessment of water distribution, especially if the prediction equations were developed with CKD patient data. We assess the correlation blood pressure with water distribution in a chronic kidney disease (CKD) multi-ethnic Asian population.

Method:
We prospectively recruited stable CKD patients and measured systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) using CARESCAPE V100, DINAMAP GE Healthcare, according to practice guidelines. Water distribution (total body water, TBW; extracellular water, ECW; intracellular water, ICW; ECW/TBW and ECW/ICW) was measured using Fresenius Body Composition Monitor by bioimpedance spectroscopy.

We used standard statistical tests where appropriate, and linear regression to assess the associations of blood pressures with the bioimpedance measures of water distribution.

Results/Expected results:
There were 104 CKD patients with mean age 59.56 + 13.09 years; comprising of 51.92% male, 71.15% Chinese, 12.50% Malay, 8.65% Indians and 7.70% Others. The mean arterial pressure was 95 +11 mmHg and the systolic and diastolic blood pressure was 138 + 18mmHg and 74 +10 mmHg respectively. The mean ECW/TBW and ECW/ICW were 0.47 +0.03 and 0.90 +0.11 respectively.

Overall, SBP is associated with ECW/TBW (p<0.001, r=0.38) and ECW/ICW (p<0.001, r=0.37).

Comments:
By bioimpedance spectroscopy, only SBP is associated with parameters of water distribution, ECW/TBW and ECW/ICW ratio.
Pharmacokinetic Characterisation Study On Pre- And Post-Dialysis Administration Of Aminoglycosides (AG) In Hemodialysis Patients

PI: A/Prof Wong Kok Seng
Affiliation: Department of Renal Medicine, Singapore General Hospital
Expected completion date: December 2014

Aims/Objectives:
The optimal aminoglycoside (AG) dosage regimen for dialysis patients has not been established [1]. Recent studies recommend pre-dialysis as it allows larger doses to be administered, maximising serum peak concentration and concentration-dependent bactericidal killing while the subsequent rapid dialytic clearance minimises overall AG exposure, reducing the risks of toxicity and adaptive resistance [1-4]. However, this strategy is logistically challenging in the local setting when patients’ dialysis times are subject to changes and availability of dialyzers. Hence, another strategy is to infuse AG at the beginning of dialysis but the pharmacokinetics of this strategy has not been established.

This prospective study aims to characterize and compare the pharmacokinetics (PK) of gentamicin and amikacin when infused post-dialysis and at the beginning of hemodialysis (HD). Secondary objectives include determination of dialytic clearance of AG and description of clinical outcomes of each patient.

Method:
Twenty adult patients with stable ESRF, on regular weekly HD and requiring AG therapy for susceptible infections in Singapore General Hospital, will be recruited for each AG and dosing strategy. Informed consent will be obtained before the first AG dose. Pregnant patients and patients receiving AG for treatment of Gram-positive infections or prophylaxis will be excluded.

PK models will be developed using a non-linear mixed effects modeling software. Blood samples will be collected at the beginning of HD (t = -2 to 0h), 30 minutes post-AG infusion (t = 1h), midpoint of HD session (t = 2h), end of HD (t = 4h), 3 hours after the end of HD (t = 7h) and just before the 2nd AG infusion. Clinical outcomes, such as duration of antibiotic therapy, eradication of infection, adverse events (ototoxicity) and overall-deaths, will be collected.

Results/Expected results:
The PK models will be used to establish pre-dialysis dosing regimens for our local hemodialysis patient population.

Comments:
Subject recruitment is on-going.

References:


Catheter-Based Renal Sympathetic Nerve Ablation For Treatment-Resistant Hypertension In Patients With Chronic Kidney Disease

PI: Dr Tan Chieh Suai
Affiliation: Department of Renal Medicine, Singapore General Hospital
Expected completion date: December 2014

Aims/Objectives:
Recent clinical studies in Western populations have demonstrated that catheter based renal sympathetic denervation (RSD) is safe and effective in treating hypertension. Although patients with chronic kidney disease (CKD) are known to have increase in activity of the sympathetic nervous system, there is limited data on the efficacy of RSD in patients with CKD. The aims of our study are:

1. Observe the magnitude and durability of the change in systolic blood pressure achieved after catheter-based renal sympathetic nerve ablation in the treatment of hypertensive patients with Chronic Kidney Disease in our local population.
2. Delineate the pathophysiological mechanism that mediates reduction in blood pressure by examining the effect of renal sympathetic nerve ablation on proteinuria, urinary sodium excretion, serum renin-aldosterone levels, renal function and metabolic profile in patients with Chronic Kidney Disease.

Method:
This is a phase 2, single arm interventional study involving 20 patients with CKD (estimated glomerular filtration rate 30 to 60mls/min/1.73m2 and treatment resistant hypertension (systolic blood pressure > 160 mm Hg despite 3 or more anti-hypertensive agents). Symplicity® Catheter will be used for RSD and the patients will be followed up for 12 months to delineate the benefits of the procedure.

Results/Expected results:
To date, one patient had undergone the procedure and completed 1 year of follow up with encouraging results. Specifically, restoration of nocturnal dipping post RSD was observed and the effect was sustained up to 12 months of follow up.

Reducing Frequent Attendance By Chronic Kidney Disease Patients At The Emergency Department

PI: A/Prof Marcus Ong Eng Hock
Affiliation: Department of Emergency Medicine, Singapore General Hospital, Office of Clinical Sciences, Duke-NUS Graduate Medical School
Expected completion date: December 2014

Aims/Objectives:
Patients with chronic kidney disease often face a multitude of issues in the course of their treatment. It is therefore important to optimize the care they receive in the outpatient setting so as to reduce non emergent users of emergency services.

Method:
This is a retrospective descriptive study, with observational data obtained from ED records for a period of 1 year.

Frequent attenders are defined as patients who have had four or more visits at the Singapore General Hospital between Jan 1 2010 to Dec 31 2010. Information collected included demographic characteristics, socio-economic profile and clinical information of each attendance.

Results/Expected results:
A total of 105, 616 patients attended the emergency department in 2010. Of the 875 patients with chronic kidney disease, 264 (30.1%) were frequent attenders and were responsible for 1881 visits. 52% of these patients were females with a mean age of 65 years old (SE 0.81%) and 64.4% were Chinese. 88.3% of the patients had at least 4 underlying co morbidities and 87% of the patients had End Stage Renal Failure. Patients presented with complaints such as blocked catheter, hypotension and anemia. 57.9% of the visits were self-referrals and 36% were referrals from dialysis centers. While 58% of the patients were triaged as priority 2, only 11% required surgical interventions.

Comments:
Frequent attenders contribute to overcrowding and increased workload at the emergency department. The most common complaints in patients with chronic kidney disease were issues with arterio-venous fistulas and prosthetic devices. A large number of visits were self-referrals, indicating the need for more patient education with regards to the available primary care institution that would be more appropriate to manage their needs.
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 2015

Aims/Objectives:
Non-adherence is a real threat to graft survival in renal transplant patients. In our 19-year experience of 38 paediatric renal transplantations in Singapore, medication non-adherence contributing to rejections is a major cause of graft failure. Adolescents have the highest non-adherence rates compared to patients of other age groups. The most important factor preventing medication adherence is the medication regime competing with rigorous school schedules and personal lifestyles. The use of telemedicine to promote adherence has been effective in patients with diabetes mellitus and asthma, but has not been studied extensively in post-renal transplant patients. We aim to study if telemedicine can improve medication adherence among paediatric renal transplant patients known to have poor medication adherence. We hypothesize the use of telemedicine intervention will improve medication adherence in these patients.

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 predetermined times to patients to remind them to take their medications on time. Patients will have to reply to acknowledge the message or to ask for a reminder. This intervention will be implemented over three months. Drug levels and estimated glomerular filtration rates will be collected before the study and at 3 months after implementation. The primary outcomes will be the percentages of times drug levels are below detectable levels and therapeutic or target drug levels are achieved. Secondary outcomes include estimated glomerular filtration rates, number of rejection episodes, quality of life, hospitalization days, and graft survival. McNemar test will be used to compare the matched proportions before and after intervention.

Results:
Fifteen post-renal transplant patients (mean age 16.01±3.86 years and mean duration post-transplant 4.78±3.75 years) with known poor history of medication adherence have been recruited. This study has been implemented for two months so far. A total of 50.3±11.2 messages have been sent to each patient per month. The patients replied to 37.6±0.3% (range 0 to 87.5%) of the messages.

Comments:
This study is still ongoing. Response rates to the SMS messages have been less than expected.
**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:** Division of Nephrology, Department of Medicine, National University Hospital  
**Expected completion date:** June 2015

**Aims/Objectives:**
To compare the performance and safety of heparin-grafted AN69 membrane (oXiris, Gambro) with the conventional AN69 membrane (M150, Gambro), 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 to 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. Circuit lifespans and post-circuit coagulation profile during use of either membrane will be compared.

**Results/Expected results:**
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 termination with either membrane; circuit trans-membrane pressures and arterial/venous pressures with either membrane; effluent:serum urea and creatinine ratios 4 hours into circuit commencement with either membrane; and vasopressor/inotropic score and urine output pre- and post- first filter with either membranes.

**Comments:**
This study will provide us with pilot data of the clinical utility of heparin-grafted membrane as a simple alternative to prolong circuit lifespan in critically ill patients who cannot otherwise tolerate systemic anticoagulation. The study is currently in progress.
Aims/Objectives:
The dialysis dependent population is increasing in Singapore. A functioning vascular access is a lifeline for these patients. The aim of this study is to examine the outcomes of hemodialysis access surgery in Singapore and to analyze factors which might influence patency of the accesses.

Method:
A prospective, longitudinal observational study of the outcome of the various types of arterio-venous fistula and graft access performed in three restructured hospitals in Singapore will be carried out. The proposed registry will enroll all patients for hemodialysis access creation from the initiation of the study for 12 months. Unlike clinical trials, the registry would reflect real life clinical situations with no specified inclusion or exclusion criteria so long as the patient is referred for hemodialysis access. Data on age, sex, diabetic status, duplex assessment, medication history, anemic status, cardiac status and prior tunneled central venous catheter (CVC) use, AV access or PD catheter use will be recorded and analyzed. Important outcomes including: mortality, access related hospital admission, access flow, vascular access failure, access related complications and procedure to salvage failing or failed access will be assessed. Primary, assisted primary and secondary patency rate will be determined using the Kaplan-Meier method.

Expected results:
There will be approximately 300 eligible potential patients to recruit and the uptake rate is expected to be high. Success rate of hemodialysis accesses and association factors analysis will be available in the last quarter of 2014.

Comments:
The result of current study will provide information on the status of hemodialysis access situation in Singapore and guild further improvement in the future.
The Effectiveness Of Self-Efficacy Psychoeducational Intervention To Enhance Outcomes Of Patients With End Stage Renal Disease: A Randomised Controlled Trial

PI: Dr He Hong-Gu
Affiliation: Alice Lee Centre for Nursing Studies, Yong Loo Lin School of Medicine, National University of Singapore
Expected completion date: June 2015

Aims/Objectives:
The study aims to examine the effectiveness of self-efficacy psychoeducational program on primary outcome (self-efficacy) and secondary outcomes (psychological wellbeing, treatment adherence, and quality of life) in patients with end stage renal disease and haemodialysis in Singapore.

Method:
A randomised controlled, two-group pretest and repeated posttests design will be adopted in the study. Patients with end stage renal disease and haemodialysis, who are above 21 years old and attend to renal clinics in one of tertiary hospitals in Singapore, will be recruited. Participants in the control group will receive a routine treatment. The participants in the intervention group will receive a self-efficacy psychoeducational intervention in addition to the routine treatment. Validated and reliable instruments (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) and interviews will be used for outcome measures at baseline, immediately post-intervention, 1- and 3-month follow-up periods. Quantitative data will be analysed using SPSS21.0 software. Qualitative data will be analysed by content analysis.

Results/Expected results:
We expected that when compared to the control group, patients in the intervention group receiving self-efficacy psychoeducational intervention will:
1. report higher level of self-efficacy in self-care behaviour;
2. report lower level of anxiety and depression;
3. demonstrate better treatment adherence; and
4. report better quality of life.

This study will identify a clinically useful and potentially effective approach to help patients with end-stage renal disease and haemodialysis by enhancing their self-efficacy in self-care behaviour, and therefore improving their psychological wellbeing, treatment adherence and quality of life. This study will provide information to develop clinical guidelines to improve patients’ disease self-management and to enhance health-related outcomes. Hopefully it will help reducing disease burden.
Aims/Objectives:
The specific aim for this study is to develop a thermo-responsive core-shell magnetic nanoparticle system for controlled release of chemotherapeutic drugs at elevated temperatures.

Renal cell carcinoma (RCC) is the most common malignant tumor arising in the kidney and surgery is currently the only effective way of treating it. It has been reported that chemotherapeutic drugs have limited treatment efficacy. However, studies have shown that heat can improve the efficacy of chemotherapeutic drugs. Therefore, in this study, we propose to utilize the synergistic effects of a combined hyperthermia and chemotherapy treatment for treating RCC. This is achieved through a thermo-responsive core-shell magnetic nanoparticle system which can generate heat under an alternating magnetic field; as temperature rises, the system will release a heightened amount of the loaded drugs.

Method:
We prepared the superparamagnetic Fe3O4 nanoparticles using co-precipitation method. Subsequently, a thermoresponsive polymer is coated onto the magnetic nanoparticles via a specific crosslinker.

We have loaded the polymer with methylene blue to perform the loading and release investigation.

Lastly, the polymer-coated Fe3O4 nanoparticles suspended in water were subjected to external heating under various magnetic field strength and the time taken for the nanoparticles to heat up to the desired temperature was determined.

Results/Expected Results:
The size of the superparamagnetic Fe3O4 core ranges from 10-20nm. The polymer that is coated onto the nanoparticles via this crosslinker is very stable and will remain on the nanoparticle. TGA analysis showed that polymers synthesized by the new method constitute up to 25% of the hydrogel coated Fe3O4 nanoparticles. The polymer was created using two different monomers. We have identified the various ratios of the starting monomers to create polymers that exhibit different lower critical solution temperature (LCST) between 34°C to 50°C, which enable us to manipulate drug release in response to temperature.

We have established the parameters to create an alternating field that can maintain our nanoparticles suspension at the hyperthermic temperature (42°C) for a duration of at least 30 minutes which is approximately the length of a hyperthermia therapy session.
Biomarkers To Predict Tenofovir Related Renal Toxicity

PI: Dr Lawrence Lee Soon-U
Affiliation: Investigational Medicine Unit, National University of Singapore
Expected completion date: December 2014

Aims/Objectives:
Tenofovir is increasingly being prescribed as first-line therapy and prevention of HIV and hepatitis B infection. Evidence is accumulating that tenofovir causes significant renal toxicity through damage to renal tubular cells, causing Fanconi syndrome, possibly by oxidative damage to renal tubular cell mitochondria. This can lead to renal failure and osteoporosis. The widespread use of lifelong tenofovir will increase the burden of renal toxicity in Singapore and globally.

The overall aim of this research programme is to prevent tenofovir-related renal toxicity. This will be accomplished by exploring toxicity mechanisms, discovering early tubular damage biomarkers and finding predictors of tenofovir toxicity.

Method:
We plan complementary laboratory and clinical research programmes. The clinical study will involve recruiting HIV patients from the clinic and existing cohorts. Blood and urine will be assayed for established and novel biomarkers of renal toxicity. These biomarkers will be compared between the tenofovir toxic group and controls without tenofovir toxicity. We will also correlate these markers with potential predictors of renal toxicity such as genetic polymorphisms and transporter function. The laboratory study will expose human kidney proximal tubule cells to tenofovir, cidofovir and adefovir. Mechanisms of tubular damage will be elucidated by measuring biomarkers of oxidative damage and apoptosis from these cells.

Results/Expected results:
We have finished recruiting 10 HIV patients who starting tenofovir as part of their anti-retroviral therapy regimen. Blood and urine samples were obtained at baseline (before starting tenofovir), 4 weeks and 12 weeks after starting tenofovir. From these samples, we expect to discover biomarkers of renal toxicity. These biomarkers can then be validated and then applied prospectively.

Calcijek® Supplementation & Vitamin D3 In Mediating Susceptibility To Fungal Infection

PI: Dr Louis Chai
Affiliation: Division of Infectious Diseases, Department of Medicine, National University Health System
Expected completion date: December 2014

Aims/Objectives:
Vitamin D3 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 D3 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 D3 (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 D3 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 D3 conferred resistance against candidemia associated with accentuated proinflammatory cytokine response. On the other hand, high dose vitamin D3 mediating an anti-inflammatory profile was non-beneficial.
Aims/Objectives:
Systemic lupus erythematosus (SLE) is an autoimmune disease predominantly affecting women in the reproductive age group. It is characterized by breakdown in tolerance, production of auto-antibodies and inflammation of multiple organs. Renal involvement with lupus nephritis (LN) contributes significantly to morbidity, with an estimated 10-15% of patients with LN developing end stage renal failure. Immune and genetic markers that can predict patients at risk will be of clinical importance.

We therefore aim:

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

2. To evaluate the effects ITGAM polymorphism on receptor expression and functional biology in LN.

Method:

1. Patients with and without nephritis will be identified from our longitudinal study cohort. Variables captured at study visits include:
   (a) Current and previous disease manifestations; (b) Disease activity scored using SLAM-R and SLEDAI (which includes urine sediment, proteinuria, and creatinine); (c) Damage index SLICC; (d) Co-morbidities such as hypertension; (e) Therapy, and (f) Paired serum/urine sample stored for assay of potential biomarkers.

2. Patients with lupus nephritis will be categorized by:
   (i) Activity of nephritis in terms of: (a) Activity of urine sediment by SLAM-R and SLEDAI; (b) Nephritic flare (active urine sediment defined as presence of cellular casts or >10rbcs/hpf, increase in proteinuria, stable or increased creatinine), and (c) Nephrotic flare (increase in proteinuria).
   (ii) Clinical subsets: (a) Asymptomatic microhaematuria+/-proteinuria; (b) Nephritic syndrome; (c) Nephrotic syndrome; (d) Nephritic-nephrotic syndrome, and (e) RPGN (rapidly progressive GN).
   (iii) Clinical course: (a) Renal non-relapsers (no renal relapse); (b) Recurrent relapsers (≥ 1 renal relapse), and (c) Refractory (recurrent relapsers) despite appropriate conventional therapy e.g. while on IV cyclophosphamide or mycophenolate.

Paired urine and serum samples will be stored at -80°C in multiple aliquots before ELISA. Serum and urine levels of inflammatory molecules including sVCAM-1, MCP-1, CXCL16, sTNFR1 and other biomarkers will be determined by ELISA according to manufacturers’ recommendations (BD Biosciences, R&D Systems).

Results/Expected results:
To be determined.

Comments:
Data collection and analysis still ongoing.
Improving Outcomes in Patients With Coexisting Multimorbid Conditions – The Development and Evaluation of the Combined Diabetes and Renal Control Trial (C-DIRECT)

PI: A/Prof Konstadina Griva
Affiliation: Department of Psychology, National University of Singapore
Expected completion date: June 2015

Aims/Objectives:
Diabetes mellitus (DM) is the most common cause of End Stage Renal Disease (ESRD). Diabetic patients on dialysis have worse clinical outcomes and increased psychological burden. The need to manage the combined treatment demands for both conditions is particularly challenging yet there is paucity of data on the barriers preventing optimal management. Better control and quality of life can be achieved through identifying these drivers and through an intervention, which modifies health behaviors and coping strategies. The significance is to reduce the individual's burden of these co-existing diseases and their associated complications, without significantly increasing the costs on health services. This project seeks to develop and evaluate the effectiveness of an intervention [Combined Diabetes and Renal Control Trial – C DIRECT] to enable people with diabetes and ESRD to better manage both their conditions.

Method:
THE C DIRECT project comprises a mixed method observational study (Stage 1) and a feasibility trial (Stage 2). The observational study will be first initiated to document outcomes and needs of the population (patients with Diabetic Nephropathy and ESRD) and seek input on preferred delivery/implementation for the program. Data will be collected with in-depth interviews (N=20) and questionnaire-based survey of DM ESRD patients (N=100). Input on content and delivery of program will also be sought by renal and allied health care professionals (N=10) and family members that are involved in patients' care at home (N=20) using interviews.

Stage 2 will build upon these data to design and test feasibility a practical, low-intensity, clinic-integrated intervention using a self-management paradigm. The C DIRECT intervention will primarily seek to support behavioral change so as to improve adherence and clinical outcomes for both DM and ESRD (i.e., glycemic and phosphate control metabolic parameters) so as to prevent complications. Secondary outcomes will be emotional adjustment and Quality of Life. For the feasibility trial, we will be evaluating acceptability, retention and completion rates of the C DIRECT program. A total of N = 30 patients randomly allocated to C DIRECT or usual will be recruited for the feasibility trial.

Results/Expected results:
C DIRECT has received ethics approval and data collection for the observational mixed methods study (Stage 1) is currently under way. It is anticipated that this will be completed by the 3 quarter of 2014 and that the C DIRECT feasibility trial will be launched in 2015.
Role Of Angiomotin In The Pathogenesis Of Membranous Nephropathy

PI: Dr Isaac Liu Desheng
Affiliation: Department of Pediatrics, National University Health System
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.

We have identified a mutation in AMOT, the gene coding for angiomotin, via exome sequencing in a family with X-linked membranous nephropathy and anti-tubular basement membrane disease, presenting as steroid-resistant nephrotic syndrome, microscopic haematuria and Fanconi syndrome.

Our primary hypothesis is that the mutation in the AMOT gene is functional. Our secondary hypothesis is that the anti-glomerular/TBM antibodies present in the family are anti-AMOT. Extrapolating from the Heymann nephritis model, we postulate that mutant angiomotin in glomeruli and proximal tubules is an autoantigen target, resulting in the formation of autoantibodies and their deposition on the glomeruli and proximal tubules.

Method:
Our specific aims, therefore, are to:

1. Study the expression of angiomotin in human and rat kidneys.

2. Elucidate the effects of the angiomotin mutation by its transfection into podocytes, tubular and endothelial cells and observing its effects on cell morphology, interaction with binding partners, cell migration, and stabilization of endothelial tubes.

3. Confirm the identity of anti-TBM antibodies present in the index family as anti-AMOT antibodies.

4. Elucidate the in vivo effects of mutant amot using a zebrafish model.

Results/Expected results:
We expect to find that mutant angiomotin has downstream effects on cell morphology, migration and stabilization of endothelial tubes. We expect to confirm the identity of pathogenic anti-TBM antibodies in the family being studied.
ACKNOWLEDGEMENTS

The National Kidney Foundation would like to thank the following for their support and contributions:

The late Venerable Yen Pei, the leader of Singapore Buddhist Welfare Services and its devotees for their generous contribution to research in renal-related diseases

Prof John Wong, Isabel Chan Professor in Medical Sciences, Chief Executive, National University Health System, Senior Vice President, Health Affairs, National University of Singapore, for his kind presence as the Guest-of-Honour

Prof Karl Tryggvason, Tanoto Professor of Diabetes Research, Cardiovascular & Metabolic Disorders Program, Duke NUS Graduate Medical School, for his kind presence as a Judge for the Abstract (Oral and Poster) Presentations

A/Prof Evan Lee, Senior Director, Clinical Services Division, National Kidney Foundation, Senior Consultant, Department of Medicine, Nephrology, National University Health System, for his kind presence as a Judge for the Abstract (Oral and Poster) Presentations

Dr Chionh Chang Yin, Head and Consultant, Department of Renal Medicine, Changi General Hospital, for his kind presence as a Judge for the Abstract (Oral and Poster) Presentations

Dr Mooppil Nandakumar, Director, Medical Services, National Kidney Foundation, for delivering The NKF Lecture

Prof A. Vathsala, Chairman, NKF Research Committee, Head & Senior Consultants, Department of Medicine, Nephrology , National University Health System, for her kind presence as a Chairperson for the Plenary Lectures

A/Prof Lina Choong, President, Singapore Society of Nephrology, Senior Consultant, Department of Renal Medicine, Singapore General Hospital, for her kind presence as a Chairperson for the Oral Presentations.

Dr Terence Kee, Chairman, Chapter of Renal Physicians, Senior Consultant, Department of Renal Medicine, Singapore General Hospital for his kind presence as a Chairperson for the Moderated Poster Session

And all those who have contributed in one way or another to the success of the 2nd NKF Scientific Meeting.
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