Welcome to this review of the 51st Annual Scientific Meeting of the Australian and New Zealand Society of Nephrology held in Canberra on 7-9 September 2015.

This review has been created to allow those unable to attend, but with a keen professional interest, to access a summary of some of the presentations. Selection and review of the research has been carried out independently by Associate Professor Martin Gallagher of Concord Clinical School at the University of Sydney who attended the meeting.

Abstracts for the selected presentations were published in a special issue of Nephrology (Volume 20, Issue Supplement S3) in September 2015 and we have provided links to these in the text. We hope you enjoy these selections, and as always, look forward to hearing your comments and feedback.

Kind Regards,

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Detecting bowel cancer in chronic kidney disease – the DETECT study

Authors: Wong G et al.

Summary: The goals of the international multi-centre DETECT study included establishing the prevalence of advanced colorectal neoplasms in adults with CKD and examining the efficacy of immunochemical faecal occult blood testing (iFOBT) as a method of screening. Participants aged 35-74 years were screened with two iFOBTs and those with ≥ 1 positive results received colonoscopy. Amongst the 1,602 subjects, 45.8% had stage III-V CKD, 24.7% were receiving dialysis and 29.7% had received a kidney transplant. Positive iFOBT screening results were obtained for 21.5% of subjects. During follow-up 7 patients developed colorectal cancer and 101 developed advanced colorectal adenomas, with 58% (n = 63) being located in the sigmoid and transverse colon. Prevalence rates for advanced colorectal neoplasms were 5.7% (95% CI 4.3, 7.6) in subjects with stage III-V CKD, 5.9% (5.6, 11.0) in those receiving dialysis. iFOBT had a positive predictive value of 35.4% (29.9, 41.3) in screening for advanced colorectal neoplasms.

Comment: This study has been a long-standing initiative from the research group at Westmead Hospital trying to understand the performance characteristics of faecal occult blood testing screening in patients with kidney disease. Patients with CKD have higher rates of cancers and may be more likely to have occult bleeding as well, both of which may well have material impacts upon the value of screening programmes for bowel cancer. The main finding from this preliminary analysis was that the prevalence of advanced colorectal cancer appeared to be higher in patients with CKD than in the general population but, perhaps more importantly, false positive rates were similar to those seen in the general population. We await the full results of this study with great interest.

Abbreviations used in this review:

ADPKD = autosomal dominant polycystic kidney disease; CKD = chronic kidney disease; MPO = myeloperoxidase; SLE = systemic lupus erythematosus; WGS = whole genome sequencing.
Complement acting through the C5α receptor mediates anti-myeloperoxidase auto-immunity and glomerulonephritis

Authors: Dick JSC et al.

Summary: These researchers investigated the role of complement acting via the cellular receptor for C5α (C5AR) in anti-myeloperoxidase (MPO) autoimmunity and glomerulonephritis utilising murine models. In C5AR-/- mice T cell proliferation was reduced vs wild type (5H-thymidine 574 ± 123 vs 1302 ± 253 counts per minute; p = 0.01) indicating MPO autoimmunity was significantly attenuated. Reductions in Th1 response (p = 0.03) and footpad delayed-type hypersensitivity were also observed (p = 0.001), but Th17 response was unaffected. CSAR-/- mice also exhibited a significantly greater proportion of CD4+ cells which were CD25+Foxp3+ T regulatory cells (p < 0.001). In a separate experiment mice with induced anti-MPO glomerulonephritis who were injected with CSAR-/- MPO-pulsed bone marrow derived dendritic cells had significantly reduced renal injury (segmental glomerular necrosis 9.9% ± 2 vs 30.9% ± 5 (p = 0.005) vs those who received wild type cells.

Comment: This research came out of the Centre for Inflammatory Diseases at Monash University and uses a mouse model for looking at ANCA-associated vasculitis. The current treatments for this condition are fairly blunt and have significant potential risks for patients. This series of experiments is strongly suggesting that the C5A receptor, primarily through action upon dendritic cells, is important in generating the inflammatory response to this condition. This opens a potential door in the future to treatments directed at this receptor as being effective strategies for this and potentially other autoimmune diseases. Whilst it is quite long a way from the bedside at the moment it's an interesting insight into future possible treatment strategies.

Effects of a 3-year lifestyle intervention on cardiorespiratory fitness and exercise capacity in patients with chronic kidney disease

Authors: Beetham KS et al.

Summary: This long-term randomised study assessed the benefits of a primarily home-based lifestyle intervention (LI) on cardiorespiratory fitness and exercise capacity vs standard care in patients with CKD. Subjects (n = 94) had stage III-IV CKD. Those randomised to LI received an individualised gym-based exercise intervention (6 weeks) followed by a home-based programme (34 months), and could receive gym refresher sessions or follow-up phone calls monthly or as needed. The proportion of subjects in the LI group who met physical activity guidelines of > 150 minutes of moderate intensity exercise per week had increased from 31.3% at baseline to 62.2% at 36 months. Subjects who received LI had significantly increased exercise capacity at 36 months vs controls; median metabolic equivalents of +2 (IQR 3.4) vs -0.6 (1.8), p = 0.01. Median cardiorespiratory fitness (VO2 peak) increased with LI from 21.0 (7) mL/kg/min at baseline to 25.4 (5.4), 23.5 (7.4) and 22.2 (6.3) at 12, 24 and 36 months respectively, but decreased with standard care by -3.7 (5.2), p < 0.001 at 36 months.

Comment: This research from the University of Queensland addressed one of the challenges in patients with CKD, that of developing sustainable interventions that have long-term impacts upon behaviour and health. This study had broad inclusion criteria, including patients with stage III and IV CKD and their baseline exercise capacity was very low. The intervention was associated with large changes in physical activity and exercise capacity, especially in the first 12 months. Unfortunately there was quite a lot of dropout over time (mainly due to funding challenges) but this data would suggest that physical activity may have large effects upon important surrogate markers of cardiovascular fitness and risk.

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FOSRENOL is indicated for the treatment of hyperphosphataemia in adults with chronic renal failure on haemodialysis or continuous ambulatory peritoneal dialysis.
Autosomal dominant polycystic kidney disease – utilisation of whole genome sequencing to identify PKD1 and PKD2 mutations

Authors: Mallawarachchi A et al.

Summary: Autosomal dominant polycystic kidney disease (ADPKD) arises from mutations in PKD1 and PKD2. These researchers report the first use of whole genome sequencing (WGS) in order to generate a molecular diagnosis in 26 patients (23 unique pedigrees) with clinically diagnosed ADPKD. They conducted 150 bp paired-end sequencing (Illumina HiSeq X sequencer) and used in-house techniques to align reads to the reference genome. Variant analysis was targeted to PKD1 and PKD2. In 22/24 (92%) patients a pathogenic variant was identified. All were confirmed with long-range PCR amplification followed by Sanger Sequencing. No false positives were observed.

Oral Abstracts: abstract #115

Comment: These 2 abstracts represent some early work in the greater exploration of the genetics of kidney disease. Whilst probably not of immediate clinical relevance they offer a glimpse of how this area may change our thinking and therapeutic approaches. The first of them from Dr Simon Jiang at ANU used a number of techniques including whole genome sequencing to first identify candidate genes in a small SLE patient population and then analyse the effects of these mutations in animal cell lines. The outcome was the identification of a rare genetic variant (BANK1) that may form the basis of up to 6% of SLE in the population. The 2nd abstract from Dr Amali Mallawaarachchi at the Garvan Institute also used WGS as a way of obtaining a molecular genetic diagnosis in patients with ADPKD. Most patients with this condition never have a molecular diagnosis due to the challenges of existing testing methods. Using a cohort of 26 patients the investigators demonstrated that WGS is likely a comprehensive and reproducible method in this patient population with implications for family planning, donor selection, diagnosis in younger patients and better estimation of prognosis. The door to the role of genetics in kidney disease is now being opened, and these 2 abstracts illustrate some of the early glimpses of what we might find.

BANK1: a critical genetic determinant of B-cell systemic lupus erythematosus

Authors: Jiang S et al.

Summary: These authors aimed to identify rare (minor allele frequency < 0.02) genetic variants associated with systemic lupus erythematosus (SLE) using whole genome sequencing of affected probands from the APOFLEC SLE cohort. Effects of the mutations were examined in functional assays including human inflammatory cytokine cytokine cytometric bead assays, co-immunoprecipitation and luciferase systems. Subjects in the SLE cohort had an increased frequency (6%) of a rare mutation in B-cell scaffold protein with angiokinase rapeseed (BANK1) compared to an expected frequency of 0.5%. Subjects with BANK1 mutations also carried other rare/novel BANK1 signalling pathway mutations which were demonstrated to have damaging effects. These included a Blk mutation which inactivates Blk kinase resulting in decreased BANK1 phosphorylation and an IRAK2 mutation which increased TLR signalling and TRAF6-mediated IL-6 production (characteristic of immortalised B-cells in SLE patients with BANK7 mutations).

Young Investigator Awards: abstract #20

Abstract

Normal saline versus lower-chloride solutions for kidney transplantation

Authors: Wan S et al.

Summary: The aim of this systematic review was to determine the impact of lower-chloride content balanced electrolyte solutions (BES) on delayed graft function, hyperkalaemia and acid-base status in kidney transplant recipients. The authors utilised the Cochrane Renal Group’s specialised register to identify 6 RCTs (n = 477 adults, 70% live donor transplant) which compared perioperative BES with normal saline (NS). In subjects who received BES risk of delayed graft function (RR 1.03: 95% CI 0.62, 1.70; p = 0.91) and hyperkalaemia (RR 0.48: 0.04, 6.10; p = 0.57) was not different to that in recipients of NS. Differences observed in the BES cohort vs NS included higher pH (mean difference 0.07: 0.05, 0.09; p < 0.00001) and bicarbonate (HCO3- 3.04 mEq/L: 2.13, 3.94; p <0.00001) and lower chloride (-9.93 mmol/L: -19.96, -0.11; p = 0.05). The authors noted that despite a reduction in hyperchloroaemic metabolic acidosis in BES recipients, clinical events were not reduced.

Oral Abstracts: abstract #080

Abstract

Effects of intravenous iron carboxymaltose versus iron sucrose on fibroblast growth factor-23 in patients receiving dialysis

Authors: Huang L et al.

Summary: This randomised controlled clinical trial assessed the impact of iron carboxymaltose vs iron sucrose on serum concentrations of sFGF-23 in anuric patients receiving haemodialysis 3x per week who required iron replacement. Subjects (n = 28, mean age 70.1 years, 75% male) underwent 1:1 randomisation to a single 200 mg IV dose of ferric carboxymaltose (FCM) or iron sucrose (IS). Serum sFGF-23 concentrations (as determined by ELISA) decreased by 23.2% (± 3.9) at 7 days post-FCM administration (p < 0.0001); the reduction was maintained to Day 21 but returned to baseline by Day 42. Administration of IS did not alter serum sFGF-23 levels. Other changes observed included decreases in serum phosphate at 48 hours with both formulations, which was maintained out to Day 7 with FCM only (-6.4% ± 1.7; p < 0.001). Serum calcium and parathyroid hormone levels were not clearly affected by either treatment.

Oral Abstracts: abstract #101

Abstract

RESEARCH REVIEW Making Education Easy

Treatment adherence in clinical trials evaluating cardiovascular or mortality outcomes in dialysis patients

Authors: Murali K et al.

Summary: The authors of this systematic review aimed to determine the methods of assessment and reporting of medication non-adherence in clinical trials, and its impact on cardiovascular and mortality outcomes in dialysis patients. They identified 21 RCTs (11 placebo-controlled) published between 2005 and 2015 from MEDLINE, EMBASE and Cochrane CENTRAL databases (encompassing 19,212 dialysis patients) which reported clinical cardiovascular or mortality outcomes. The trials tested self-administered medications including anti-hypertensives (n = 6), phosphate binders (n = 4), lipid-lowering drugs (n = 3), cardiovascular therapies (n = 3), homocysteine lowering drugs (n = 2), fsh oil (n = 2) and calcimetics (n = 1). Adherence rates, in the 5/21 trials in which adherence was reported, were between 65 and 91.7%, with pill count being the most frequently utilised method of measurement. Reporting of adherence and its relationship to study drug discontinuation (which was frequent with both placebo and intervention) was inconsistent and appeared under different headings in the publications. As a consequence of both the lack of adherence reporting and inconsistencies in the methods of reporting adherence the authors were unable to determine relationships between medication adherence and the specified outcomes.

Comment: This report tries to answer the question of whether poor adherence to study interventions is driving the lack of efficacy seen in various treatments in haemodialysis patient trials. Its findings were limited a little by the fact that the reporting of adherence is inconsistent and generally poor in clinical trials. They found that often those interventions with better adherence have higher patient dropout rates, suggesting that the dropout rate may be masking adherence problems. Whilst they didn’t find a clear impact of adherence upon study findings, this is an often neglected area in clinical trials which has the potential to have profound effects upon the value of such trials.

Oral Abstracts: abstract #053

Abstract

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Mammalian target of rapamycin inhibitors and clinical outcomes in adult kidney transplant recipients

Authors: Badve SV et al.

Summary: This retrospective analysis examined associations between the use of mTOR inhibitors in kidney transplant recipients and allograft failure and all-cause mortality. Subjects identified from the ANZDATA Registry were 10,403 adults who received kidney transplants (10,649 surgeries) between 1996 and 2012 and had allograft survival times of ≥ 1 year. Significant geographical variations in mTOR inhibitor use were observed. Factors associated with receipt of mTOR inhibitors included Caucasian ethnicity, a history of cancer and transplants received between 1996 and 2001. In multivariate Cox regression analysis using mTOR inhibitor use as a time-varying covariate all-cause mortality was increased with mTOR inhibitor use (HR 1.02; 95% CI 1.01, 1.04). However this effect was not observed in fixed-time or propensity scorematched analyses. Allograft failure risk was decreased with mTOR inhibitor use in the total cohort (HR 0.97; 95% CI 0.95, 0.99) and the propensity scorematched analyses. Allograft failure risk was decreased with mTOR inhibitor use as a time-varying covariate all-cause mortality was increased with mTOR inhibitor use (HR 1.02; 95% CI 1.01, 1.04). However this effect was not observed in fixed-time or propensity scorematched analyses. Allograft failure risk was decreased with mTOR inhibitor use in the total cohort (HR 0.97; 95% CI 0.95, 0.99) and the propensity scorematched cohort (HR 0.96, 0.94, 0.99) but was not different to controls under fixed-time models and their respective propensity scorematched cohorts.

Comment: This analysis of data from the ANZDATA Registry looked at the impact of mTOR inhibitors upon long-term transplant in patient outcomes. They divided the patient group into 4; those who never used mTOR inhibitors, those who were on mTOR at baseline those who converted to mTOR <1 year and those who converted to mTOR >1 year post transplant. There is probably some residual confounding by indication at play here so the findings should be interpreted with caution, but the analysis suggests that mTOR use may be associated with an increased risk of all-cause mortality. There was no association between mTOR use and allograft loss.

Oral Abstracts: abstract #114
Abstract

Death due to dialysis access haemorrhage: why does it happen and what are we doing about it?

Authors: Lioufas N et al.

Summary: These researchers examined reports of deaths caused by bleeding from haemodialysis vascular access. Reports of death due to dialysis access haemorrhage from 1 January 2000 were obtained from a systematic search of the National Coronial Information System (NCIS) for Australia and New Zealand, ANZDATA, State Rented Network reports, individual renal units and published cases. The total number of identified deaths was 83, mean age 67 years (range 30–89), 55% female. Twelve subjects were receiving home haemodialysis. Factors contributing to death by dialysis access haemorrhage included infection (22%), dialysis or catheter problems (17%), recent access intervention (15%) and use of a high arteriovenous fistula (11%). Use of warfarin contributed to a single death, as did cognitive impairment. Investigations into the deaths including Coronial inquests and Root Cause Analyses occurred in 7/83 cases.

Comment: This has been a topical issue in nephrology following some formal investigations by the Victorian Coroner in recent years. This group sought data from the National Colonial Information System and linked them with the ANZDATA registry. They analysed 83 deaths and almost all of these were associated with pre-existing problems with dialysis access. Whilst it’s not common, with likely around one death per year in New South Wales, it is catastrophic and only a minority of these deaths have been formally investigated. Addressing this issue will require a broad national approach, and perhaps could be something more readily addressed using national key performance indicators.

Oral Abstracts: abstract #104
Abstract

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